FAMILY STUDIES IN PATIENTS WITH THE SLEEP APNOEA /HYPOPNOEA SYNDROME

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ABSTRACT

The predisposing factors leading to the development of sleep apnoea/hypopnoea syndrome (SAHS) in many cases are unclear. Snoring, a prerequisite for SAHS, runs in families. There have been reports of familial SAHS in several families but this may have resulted from an association with obesity. I have therefore investigated whether SAHS is familial.

In a pilot study breathing and oxygen desaturation data during sleep in 40 first degree relatives of 20 non obese SAHS patients has been compared with that in retrospective controls. Ten out of 40 relatives had >15 apnoeas+hypopnoeas/hr of sleep and 8 had >5 4% desaturations/hr. These frequencies of irregular breathing ($p<0.005$) and desaturation ($p<0.0001$) are significantly higher than in the British population.

A case control study has therefore been performed examining sleep symptoms, sleep studies, upper airway calibre by acoustic reflectance and facial structure by cephalometry in first degree relatives of non obese (BMI<30 kg/m^2) patients with SAHS and matched controls drawn from a general practitioner's register.

Fifty one relatives of 32 SAHS patients were matched with 51 controls for sex (25 male), age (36 SD 14, 35 SD 14 yrs) and BMI (24 SD 4, 24 SD 3 kg/m^2) on a one to one basis. More relatives than controls reported snoring

(48% vs 12%, p=0.0002), excessive daytime sleepiness (56% vs 32%; p=0.01), sleeping against will (20% vs 4%; p=0.01), and nocturnal choking (16% vs 2%; p=0.01). Relatives had higher apnoeas+hypopnoeas per hour of sleep (median 13 vs 4/hr; p<0.0001), more arousals from sleep (median 30 vs 17/hr; p<0.0001), higher 2%/hr (p=0.04) and higher 3%/hr (p=0.04) desaturation frequency than the controls. The relatives had more light sleep (p=0.006) and less slow wave sleep (p=0.03) than the controls. The relatives had smaller pharyngeal volume (19 SEM 1, 23 SEM 1 mls; p=0.01), smaller mandibles (Go-Gn 84 SEM 1, 87 SEM 1 mm; p=0.03), retroposed maxillae (SNA angle 81 SEM 1, 86 SEM 1 deg; p<0.0001), retroposed mandibles (SNB angle 78 SEM 1, 82 SEM 1 deg; p<0.0001), longer (p=0.03) and wider uvulae (p<0.0001) than the controls.

In a pilot study to determine whether there might be any association between SAHS and Sudden Infant Death Syndrome, it was found that 8 unexpected sudden infant deaths were reported in 28 SAHS families compared to none in 35 control families (p<0.01). This preliminary observation requires independent verification.

Thus SAHS is familial and this family tendency is associated with anatomical changes which predispose to upper airway narrowing.

STATEMENT

I hereby declare that this thesis has been entirely composed by myself. I did not recruit subjects for the pilot study or score their sleep studies. I did not operate the X-Ray machines for obtaining cephalometric films. Other than these I did all the work presented in the thesis myself.

All the work presented has been done at the Scottish National Sleep Laboratory. No part of the work in this thesis has been submitted for another degree or qualification to this or any other university.

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CHAPTER 1

SLEEP APNOEA REVIEW

Introduction

Sleep apnoea/hypopnoea syndrome (SAHS) is due to repeated upper airway collapse during sleep. The upper airway includes the extrathoracic trachea, larynx, pharynx and the nasal passages. The pharyngeal component of the upper airway is limited cranially by the nasopharynx and caudally by the glottic opening. The pharynx is the final common pathway for the transmission of air, liquids and solids and therefore serves several functions like deglutition, phonation and respiration (Henderson-Smart DJ, 1984). Swallowing and phonation dictate that pharynx be a collapsible tube with co-ordinated neuromuscular actions. The pharynx is therefore, a soft tissue structure and lacks a rigid bony support (Bosma JF, 1988). As it also serves as a conduit for airflow, the pharynx is liable to inspiratory narrowing which, in some people, progresses to subtotal or total pharyngeal collapse. During wakefulness, the pharyngeal patency is largely maintained by neuromuscular activity which not only maintains a patent airway for breathing but also coordinates this with the digestive and phonatory functions of the pharynx. This supervision of the pharyngeal airway may be disrupted during sleep with resultant luminal compromise. In those with small pharynx during wakefulness (Rivlin J et al, 1984, Bradley TD et al, 1986a, Schwab RJ et al, 1993), this further

narrowing during sleep may result in severe narrowing or closure of the pharynx heralding obstructive sleep apnoea.

SAHS causes daytime sleepiness and impaired daytime performance (Greenberg GD et al, 1987, Findley LJ et al, 1986) and results in increases in road traffic accidents and mortality from cardiovascular and cerebrovascular events (Partinen M et al, 1990). Repeated upper airway narrowing during sleep results in recurrent arousal from sleep, with consequent sleep fragmentation (Bonnet M et al, 1992) and recurrent transient hypertension (Knight H et al, 1987). It occurs at least in around 0.3% of adult men (Stradling JR et al, 1991a) and may occur in upto 2-4% of middle aged men and 1-2% of middle aged women (Jennum P et al, 1992, Young T et al, 1993).

Historical aspects

SAHS is not a new disease but was described in ancient literature. Dionysius of Heracliea, the ruler and tyrant in Pontis in the era of Alexander the Great, was extremely obese. He was reported to suffer from difficulty in breathing during sleep and pathological daytime sleepiness. Long sharp needles were used to jab him in the belly to keep him awake and breathing (Wadd W, 1822).

Magas, King of Cyrene, died in 258 BC and "was weighted down with monstrous masses of flesh in his last days; in

fact he choked himself to death" (Athenaeus, 1863). In 1816 William Wadd described several cases with features suggestive of typical sleep apnoea. A good account of this disease appeared in 1837 in Charles Dicken's 'The Pickwick Papers'. The term 'Pickwickian' however was coined in 1918 by Osler in the 8th edition of his book 'The Principles and Practice of Medicine'.

In 1877, WH Broadbent published a case report in the Lancet about Cheyne Stokes breathing in a patient with cerebral haemorrhages. He noted that a similar pattern of breathing could be observed in an elderly subject especially while sleeping supine and snoring. He described 'breathing pauses' and gasps presumably due to recurrent upper airway obstruction.

R Canton, in 1889, presented to the Clinical Society of London 'a case of narcolepsy' but the clinical features described seem typical of sleep apnoea. In the same year, Morrison reported a similar case of an elderly obese man with worsening drowsiness accompanied by cyanosis, snorting and choking in sleep.

The first account of disordered breathing in sleep as a specific sleep disorder was given by SW Mitchell in 1890 when he described a patient with probable central sleep apnoea.

In 1897, L Lamacq linked upper airway obstruction with sleep disorders. In 1898 W Wells described a further 10

patients with obstructed nasal breathing 8 of whom complained of daytime sleepiness.

In 1937 Spitz described three cases with most of the clinical features of sleep apnoea. However, the relationships between sleepiness, sleep disordered breathing, polycythaemia and right sided failure were not properly appreciated.

In 1955, HO Sieker et al published the report of four patients under the title 'Cardiopulmonary syndrome associated with extreme obesity'. Though they contributed little to the understanding of the pathophysiology of the syndrome, they did reverse many aspects of the syndrome by simple weight reduction.

Though CS Burwell et al in 1956 described the a patient with sleep apnoea, it is likely that their patient had obesity related hypoventilation syndrome.

In 1966, H Gastaut performed overnight polysomnography of a Pickwickian patient and was the first to report multiple obstructive apnoeas and arousals. He concluded that the nocturnal sleep deprivation and disruption was responsible for the excessive daytime sleepiness.

In 1975 Sutton advocated the use of progesterone and in 1982, Brownell the use of protryptiline in the treatment of sleep apnoea. In 1976, tracheostomy was found to 'cure' the disease by bypassing the obstruction (Guilleminault C et al). In 1981 positive upper airway

pressure applied through the nose was shown to be effective in the reversal of sleep apnoea syndrome (Sullivan CE et al, 1981). In the same year surgical treatment of the disorder was described with uvulopalatopharyngoplasty (Fujita S et al).

Definitions

An apnoea, in adults is defined as complete cessation of oronasal airflow for at least 10 seconds (Guilleminault C et al, 1978). A validated definition of hypopnoea is a greater than 50% reduction of thoracoabdominal movement for at least 10 seconds (Gould GA et al, 1988). This definition gives a truer estimate of clinically significant hypopnoea frequency as it is significantly closer to the arousal frequency than flow related definitions. Alternative definitions of hypopnoeas like over 75% or 25% reduction in thoracoabdominal movements under and over estimate the frequency of arousals and desaturations (Gould GA et al, 1988).

Apnoea signifies complete occlusion of the upper airway while hypopnoea a nearly complete occlusion (West P et al, 1985). Hypopnoeas are as important as apnoeas in the developement of symptoms and of the sleep related desaturation and arousal characteristics in the SAHS (Gould GA et al, 1988).

The total number of apnoeas and hypopnoeas per hour slept has been termed the 'Apnoea Hypopnoea Index-AHI'. Though

the association of an AHI that is greater than 5, 10 or 15 with the development of a specific clinical picture has not been absolutely established (Phillips BA et al, 1992), our group's definition in young or middle age patients of SAHS is the presence of more than 15 apnoeas plus hypopnoeas per hour slept in conjunction with at least two major symptoms (Gould GA et al, 1988). It seems that the definitions based on an AHI of 5 (Guilleminault C et al, 1984a) or 10 (Bradley TD et al, 1985) maybe too lax and many normal subjects fulfill such criteria (Gould GA et al, 1988, Young T et al, 1993).

Pathology and pathophysiology of the SAHS

Snoring, hypopnoeas and apnoeas result from recurrent upper airway narrowing and occlusion during sleep (Remmers JE et al, 1978). Approximately half the patients with the SAHS obstruct their upper airways behind the tongue and the remaining half behind the soft palate (Hudgel DW et al, 1988, Chaban R et al, 1988). Many patients obstruct the upper airway at multiple levels during sleep (Morrison DL et al, 1993).

The upper airway intraluminal pressure during inspiration is subatmospheric and this tends to suck the pharynx closed (Harper RM et al, 1978). During wakefulness, this tendency of the upper airway to collapse is actively opposed by the upper airway dilator muscles (Wheatley JR et al, 1991). Retroglossal airway patency is maintained by the combined actions of the genioglossus, geniohyoid

and omohyoid which exhibit inspiratory phasic contractions (Sauerland EK et al, 1981, Weigand DA et al, 1990). Retropalatal patency is maintained by the muscles of the soft palate, the actions of which are still incompletely understood. Palatoglossus depresses the soft palate onto the base of the tongue and maintains a patent retropalatal airway (Kuehn DP et al, 1982) for nasal breathing, the preferred route of breathing during sleep (McNicholas T et al, 1982). Levator palatini and perhaps palatopharyngeus (Kuehn DP et al, 1982) lead to velopharyngeal closure and open the oral breathing route. Tensor palatini tenses the soft palate, opens up the auditory tube and may also retract the soft palate away from the posterior pharyngeal wall (Tangel DJ et al, 1991). However, the actions of this muscle are complex and ill understood. Some of these muscles of the soft palate may also show inspiratory phasicity during wakefulness and sleep (Hairston LE et al, 1981).

Sleep related hypotonia and relaxation of levator palatini (Tangel DJ et al, 1993) and tensor palatini (Tangel DJ et al, 1991) has recently been shown. Decreased tensor activity is thought to cause airway narrowing in the area posterior to the soft palate predisposing to apnoeas and hypopnoeas. A fall in genioglossal activity during NREM sleep in SAHS patients (Remmers JE et al, 1978) and a decrease in EMG levels of genioglossus group of muscles during apnoeas has also been demonstrated (Suratt PM et al, 1988). SAHS patients

have been shown to have higher awake genioglossal activity compared to controls. This may indicate reflex activation of genioglossus as a compensatory phenomenon (Mezzanotte WS et al, 1992). This neuromuscular compensation present during wakefulness in SAHS patients may be lost during sleep leading to airway collapse. Upper airways which are narrow when awake are more likely to narrow critically during sleep (Sauerland EK et al, 1976).

Many studies have shown that patients with SAHS have smaller upper airways than control subjects (Bradley TD et al, 1986a, Harponik EF et al, 1983, Hoffstein V et al, 1984, Rivlin J et al, 1984, Shepard JW et al ,1990, Suratt PM et al, 1985, Stein MG et al, 1987) largely due to abnormalities in bony and soft tissue craniofacial architecture. The upper airways of these patients may also be excessively compliant and floppy (Remmers JE et al, 1978). These patients have increased nasal resistance which increases the upstream airway resistance and hence increases the collapsing intraluminal pressure during inspiration (Zwillich CW et al, 1982).

Periodic breathing during sleep is a normal phenomenon (Phillipson EA, 1978). The factors contributing to periodic breathing during sleep include disappearance of wakefulness induced stimuli that obscure the normal oscillatory respiratory centre output, sleep induced changes in chemosensitivity and the changing neural

control during the instability of sleep onset (Phillipson EA, 1978). Periodic breathing induces periodic changes in the upper airway and respiratory muscle activity with wane of neural drive to both muscle groups (Onal E et al, 1982). The decrease in drive to upper airway muscles with resultant rise of upper airway resistance and higher negative inspiratory pressures for a given respiratory muscle activity leads to upper airway passive collapse (Remmers JE et al, 1978). By further increasing upper airway resistance, anatomical abnormalities of the upper airways would contribute to obstruction (Suratt PM et al, 1983). Thus, the pathogenesis of obstructive sleep apnoea may involve both central respiratory and peripheral upper airway mechanisms. A role of recurrent arousals with hyperventilation leading to hypocapnia and central apnoeas has also been proposed in idiopathic central sleep apnoea (Xie A et al, 1994).

Restoration of the patency of the near or totally occluded upper airway of these patients during sleep is achieved by an arousal which owing to its brevity is not recalled by the patient (Bonnet M et al, 1992). The arousal is caused by the large negative intrapleural pressure swing as the patient struggles to breathe against an occluded upper airway (Gleeson K et al, 1990). It is not directly a result of resultant hypoxaemia as arousal may occur without significant desaturation (Guilleminault C et al, 1988a). It may be that upon reaching a certain strength of contraction, the

inspiratory muscles trigger a reflex originated by the subatmospheric pressure in larynx, tension receptors in the chest wall, metabolic changes in the muscles (Vincken W et al, 1987) or by mechanoreceptors in the contracting respiratory muscles (Kimoff RJ et al, 1994). The sensory information from this reflex may be relayed to the central nervous system resulting in arousal. After the arousal and reestablishment of upper airway patency the subject falls asleep again with the same cycle of airway narrowing, occlusion and arousal recurring all night, especially when the breathing pattern is periodic (Onal E et al, 1982). The resultant sleep disruption and fragmentation and not hypoxaemia result in excessive daytime sleepiness (Roehrs T et al, 1989, Colt HG et al, 1991) and impaired daytime performance (Cheshire K et al, 1992, Roehrs T et al, 1994). Sleep fragmentation, and to a lesser extent sleep deprivation, in normal subjects have also been shown to increase upper airway collapsibility by reducing the upper airway dilator muscle activity either directly or via the release of endorphins (Seres F et al, 1994).

Cardiorespiratory consequences of SAHS

Normal sleep in otherwise fit subjects results in reduction in heart rate, ventilation and blood pressure. Heart rate decreases by 5-8% during NREM sleep (Khatri IM et al, 1967, Bristow JD et al, 1969) and is variable during REM with mean rates approximating resting awake

values. Mean arterial pressure decreases by 5-9% during light NREM sleep and 8-14% during slow wave sleep as compared to resting awake values (Coccagna G et al, 1971, Khatri IM et al, 1967). Arterial blood pressures during REM sleep fluctuate and are about 5% higher than immediately preceeding or succeeding values during NREM sleep. Pulmonary artery pressures during sleep stay largely unchanged (Lugaresi E et al, 1978).

Patients with SAHS have cyclical fluctuations in heart rate (Zwillich C et al, 1982), blood pressure (Davies RJO et al, 1993, Shepard JW, 1985), cardiac output (Guilleminault C et al, 1986a, Lin YC et al, 1983) and systemic oxygen delivery. These are likely to have adverse long term hemodynamic consequences.

Heart rate has been shown to be higher during post apnoeic ventilatory period than in the last few seconds of apnoea and this has been attributed to apnoeic bradycardia (Zwillich C et al, 1982b). Continuing unsuccessful inspiratory efforts against an obstructed upper airway during an obstructive apnoea lead to falls in systolic and diastolic blood pressures, the magnitude of the fall being a semiquantitative indicator of the degree of respiratory effort (Lea S et al, 1990). A recent study found falls in systolic blood pressure related to inspiration progressively increased from normal sleep, through snoring and snoring with arousals, to frank obstructive sleep apnoea (Davies RJO et al,

1993). Negative pleural pressures during obstructive apnoeas increase left ventricle afterload (Karam M et al, 1984) and at fixed lung volume increase lung blood content (Brower R et al, 1985). These, together with worsening arterial hypoxaemia, increase pulmonary arterial pressures and pulmonary artery wedge pressures during apnoeas.

With the resumption of ventilation and termination of apnoeas, the heart rate increases (Zwillich C et al, 1982b) along with a marked increase in systolic and diastolic blood pressures (Shepard JW, 1985). The post apnoeic rise in blood pressure was initially thought to be due to hypoxaemia developing during the end of apnoea (Shepard JW, 1985). Changes in cardiac hemodynamics (Parish JM et al, 1990) may also in part explain this post apnoeic blood pressure rise. However, similar blood pressure rises occur after central sleep apnoea (Davies RJO et al, 1991) where there are no intraapnoeic inspiratory efforts and also in the periodic leg movement disorder (Ali NJ et al 1991) where there are no respiratory or blood gas disturbances. All these syndromes involve recurrent arousals from sleep which are now believed to be a major cause of post apnoeic blood pressure rise (Ringler J et al, 1994).

Arousals are associated with a fall in arterial baroreceptor activity (Smyth HS et al, 1969) which leads to a rise in sympathetic neural tone (Hornyak M et al ,

1991) via the efferent limb of the baroreflex loop. This increase in sympathetic tone leads to peripheral vasoconstriction with an ensuing rise in blood pressure. The arousal induced blood pressure rise is smaller during REM than NREM sleep and arousal stimuli that do not cause EEG arousal still produce a blood pressure rise, presumably due to the activation of brain stem arousal mechanisms (Davies RJO et al, 1993).

The long term complications and associations of untreated SAHS may be systemic hypertension (Lavie P et al, 1984) though a recent study indicates that SAHS is not an independent risk factor for hypertension (Stradling JR et al, 1990a). Sleep apnoea also increases the risk of excessive vascular mortality due to myocardial infarctions (Hung J et al, 1990) and cerebrovascular accidents (Partinen M et al, 1985) probably as a result of pulsatile blood pressure disturbances during sleep (Davies RJO et al, 1994).

Symptoms

Snoring: Loud, intermittent and habitual snoring is the hallmark of sleep apnoea and is seen in 94% of SAHS patients (Whyte KF et al, 1989, Hoffstein V et al, 1993). It is a major cause of marital strife and often leads to the use of separate bedrooms.

Absence of snoring mitigates against a diagnosis of sleep apnoea but by no means excludes it. By the time of

referral snoring is usually present in all body postures rather than in supine position alone. It is often worsened after alcohol consumption.

Excessive daytime sleepiness: Present in about 88% of the cases, excessive daytime sleepiness is a major symptom of SAHS (Whyte KF et al, 1989). Many patients complaint of dozing off while watching television, reading or during other monotonous activities. Advanced sleep apnoea patients often fall asleep in the middle of a meal or conversation. They may also fall asleep while driving and there is considerable evidence that sleep apnoea is responsible for many automobile accidents (Findley L et al, 1989, Stradling JR et al, 1991, George C et al, 1987. Stradling JR, 1989).

Abnormal motor activity during sleep: 36% of the SAHS patients complain of restless sleep (Whyte KF et al, 1989) with frequent tossing and turning during the night. Some of these movements may be associated with nocturnal hypoxaemia while others may represent nocturnal myoclonus, a condition often associated with the SAHS.

Unsatisfying sleep: A combination of loud snoring and abnormal motor activity during sleep may result in disrupted sleep with frequent arousals. Many patients Bwith full blown SAHS have several hundreds of such arousals throughout the night leading to sleep fragmentation and manifesting as unrefreshing sleep in 35% of the patients.

Witnessed apnoeas: In over 70% of the cases a clear history of witnessed apnoeas is obtained (Hoffstein V et al, 1993) and the presence of apnoeas witnessed by the patient's spouse is the most useful point in the patient's history differentiating patients with SAHS from others referred for investigation (Crocker BD et al, 1990).

Nocturnal choking: Reported by 26% of patients (Whyte KF et al, 1989), this is frightening sensation which may seem to last up to a minute in duration. In most patients, arousal from sleep is immediately accompanied by upper airway patency. The choking sensation is apparently due to upper airway dilator muscle tone returning only after the patient has woken up.

Morning headaches: Diffuse or predominantly frontal morning headaches are reported by 24% of patients (Whyte KF et al, 1989) and are a non specific feature of this condition.

Irritability, nocturia and decreased libido are reported by 11%, 10% and 6% of the patients with SAHS.

Symptoms due to complications of SAHS: Secondary polycythaemia due to chronic hypoxaemia, ventilatory failure and peripheral oedema due to pulmonary hypertension, chronic cor pulmonale with congestive cardiac failure may be present in patients with long standing and severe SAHS.

The history should also enquire into alcohol consumption and whether the patient takes alcohol at bedtime. Hypnotic and sedative medicines at bedtime have an effect similar to alcohol by aggravating upper airway obstructive events. Sleep deprivation and shift work should be noted. History of smoking, respiratory allergies and of working environment should also be sought.

Physical examination

General examination: This includes noting the extent of overall obesity as well as abdominal and neck girth. Overt retrognathia, acromegaly or myxoedema should be sought. Peripheral oedema, polycythaemic appearance and the presence or absence of cyanosis should be noted.

Oronasomaxillofacial examination: On the intraoral inspection, size and consistency of the tongue, presence or absence of pharyngeal oedema, hyperaemia, appearance and size of the soft palate, length and position of the uvula and tonsillar size should be noted. Increased nasal resistance becomes obvious with inspiratory collapse of the nostril.

Diagnostic techniques

A confident diagnosis of the SAHS can only rarely be made from history (Viner S et al, 1991, Crocker BD et al, 1990) or physical examination alone (Viner S et al, 1991).

Oximetry and overnight videoing the patient

The British Thoracic Society guidelines indicate that oximetry alone or combined with video recording is sufficient to diagnose many patients with SAHS (BTS News, 1990). Visual scoring of an overnight oxygen saturation tracing is of considerable diagnostic value and permits a correct diagnosis of SAHS to be made from the characteristic desaturation pattern in up to two thirds of patients (Douglas NJ et al, 1992). A normal overnight oxygen saturation trace however does not exclude sleep apnoea and such patients with suggestive symptoms need further evaluation. Visually observing a patient at night may be sufficient to diagnose SAHS though in around a third of patients the correct diagnosis may be missed (Harponik EF et al, 1984).

Overnight polysomnography

The alleged gold standard for the diagnosis of SAHS is overnight polysomnography which, the American and Australian guidelines state, must be performed if SAHS is a possibility (Martin RJ et al, 1985 , McAvoy RD, 1988). Polysomnography confirms the diagnosis, ascertains the severity of physiological disturbance during sleep which then acts as a guide to further therapy, looks for alternative diagnoses like the periodic limb movement disorder and evaluates the response to nasal continuous positive airway pressure therapy (CPAP). Polysomnography records oxygen saturation by oximeter, thoracoabdominal

movements by impedance plethysmography, oronasal airflow by temperature or exhaled CO2 sensors, electroencephalogram, electrooculogram, submental and anterior tibial electromyogram. These techniques allow recording sleep stages and nocturnal arousals, quantitation of apnoeas and hypopnoeas and measurement of the extent of oxyhemoglobin desaturations. Polysomnography can diagnose and quantitate the leg jerks in the periodic limb movement disorder and may suggest narcolepsy by the presence of abnormally early REM sleep. The usefulness of polysomnography has recently been questioned as recording of sleep quality and duration is of little diagnostic benefit (Douglas NJ et al, 1992).

Evaluation of upper airways in SAHS

It is important to assess the upper airway to understand the pathophysiology of SAHS and to predict the efficacy of treatment.

Cephalometry: Lateral radiograph cephalometry describes craniomandibular abnormalities and soft tissue contours of the upper airways.

In a study of 10 SAHS patients, Riley R et al, 1983, showed that the cephalometric measurements of interest in patients with SAHS were uvula length, distance between mandibular plane and hyoid bone, posterior airspace and maxillomandibular discrepancies. Jamieson A et al, 1986, found that 150 Of 155 SAHS patients studied had at least

2 significant cephalometric abnormalities. They found that SAHS patients have retroposed mandibles, different cranial base flexure, inferiorly placed hyoid and longer and thicker soft palates than controls.

Strelzow VV et al, 1988, studied 90 SAHS patients and found that over 50% of the 52 cephalometric measurements were different in these patients from controls. Cephalometric measurements correlated with disease severity and could distinguish between patients with different severities of SAHS. Likewise, Partinen M et al, 1988a, found that in SAHS patients a reduction in size of posterior airspace below 5 mm and hyoid to mandibular plane distance of over 24 mm correlated with AHI irrespective of BMI. In another study of 30 SAHS patients, DeBerry-Borowieski B et al, 1988, found maxillary retrognathia, longer hard palates, abnormally low placed hyoids, small posterior airspaces, elongated lower and mid face along with thicker and longer soft palates when compared to controls. Numerous other studies have demonstrated similar bony and soft tissue differences on cephalometric examination between patients and controls (Lyberg T et al, 1989, Maltais F et al, 1991, Lowe AA et al, 1986) and some have shown that cephalometric measurements have a predictive value in determining the success rate of upper airway surgery (Guilleminault C et al, 1984b).

These reports suggest that SAHS patients have smaller

upper airways owing to differences in craniofacial anatomy. This may reduce pharyngeal dimensions at different levels and impair pharyngeal stability.

The value of cephalometric analysis, therefore, is to assist in the clinical perception of pharyngeal geometry, thereby assisting in the design and planning of a surgical procedure.

Acoustic reflectance

This technique is based on the analysis of sound waves reflected from the airway. Measurement of the amplitude of these reflections and their times of arrival at a sensing microphone permits construction of a plot of airway area versus distance from the microphone (Hoffstein V et al, 1991). It was initially used as a static technique by Rivlin J et al, 1984, who showed small pharyngeal areas in SAHS patients than in non apnoeic controls. Similar results were reported by Bradley TD et al, 1986a. Acoustic reflectance is also useful in dynamic studies to assess the effect of change of lung volume (Bradley TD et al, 1986a, Hoffstein V et al, 1984), body position and applied transmural pressure (Brown IG et al, 1985) on pharyngeal area. These results indicate that SAHS patients have increased pharyngeal compliance than controls.

Other methods for assessing upper airway size and function in these patients are computerised tomography,

magnetic resonance imaging, fiberoptic and videofiberoptic studies, cine-CT scans and measurements of upper airway pressures and resistances. To demonstrate further extent of pharyngeal collapse during sleep, somnofluroscopy and pharyngeal endoscopy under sedation have also been used.

Treatment of SAHS

General measures

Dietary control of weight may be successful in obese patients (Harman EM et al, 1982). They should be advised not to take alcohol (Krol RC et al, 1984) and sedatives (Craddock M et al, 1987) at bedtime. Patients with myxoedema, acromegaly, retrognathia or major nasopharyngeal abnormalities should be treated appropriately.

Drug treatment

Protryptiline, medroxyprogesterone and acetazolamide have been tried but have no role in the treatment of SAHS (Douglas et al, 1991).

Nasal continuous positive airway pressure (CPAP)

Since first introduced in 1981 (Sullivan CE et al), nasal CPAP has become the treatment of choice for SAHS, being effective both for obstructive and central sleep apnoea (Issa F et al, 1986). Acting as a 'pneumatic splint'(Sullivan CE et al, 1981, Popper RA et al, 1986),

CPAP maintains pharyngeal patency and eliminates apnoeas and hypopneas (Sullivan CE et al, 1984). Long term CPAP usage has been shown to improve survival (He J et al, 1988). Treatment has also been shown to improve nocturnal breathing pattern (Sullivan CE et al, 1981), nocturnal sleep quality (Sanders MH, 1984) objective daytime sleepiness (Lamphere J et al, 1989), mood (Derderian SS et al, 1988), driving (Findley L et al, 1989) and cognitive functions (Engleman HM et al, 1994a).

Surgical treatment of SAHS

Tracheostomy: Though tracheostomy cures SAHS by bypassing the upper airway obstruction and improves survival (Partinen M et al, 1988b), tracheostomy is only recommended in an emergency situation in which CPAP is unsuccessful or unavailable.

Uvulopalatopharyngoplasty: In this procedure, the posterior margins of the soft palate and the redundant lateral pharyngeal wall mucosa are resected (Fujita S et al, 1981). Though effective in curing snoring, this surgery does not cure SAHS (Wetmore SJ et al, 1986). In addition, several perioperative deaths have been reported with this procedure which anyway has not been shown to affect survival in these patients (He J et al, 1988). Some patients with failed surgery subsequently find CPAP intolerable due to the absence of an effective seal between soft palate and the tongue with resultant loss of

pressure through the mouth (Douglas NJ, 1991). For these reasons, this procedure is not advocated for treating SAHS.

Experimental procedures: Inferior saggital osteotomy with hyoid myotomy and suspension (Riley R et al, 1986a), Le Fort type 1 mandibular osteostomy (Bear SE et al, 1980, Kuo PC et al, 1979, Ferber R et al, 1983, Wittig R et al, 1983), Maxillomandibular and hyoid advancement procedures (Riley R et al, 1986b), mandibular repositioning appliances (Clark GT et al, 1993) and electrical stimulation of the tongue (Miki H, 1989, Edmonds LC et al, 1992) are not recommended routinely in the treatment of SAHS.

CHAPTER 2

RISK FACTORS AND GENETICS OF SAHS

RISK FACTORS AND GENETICS OF SLEEP APNOEA/HYPOPNOEA SYNDROME

The commonly acknowledeged risk factors for obstructive sleep apnoea are obesity, male sex, middle age, endocrine abnormalities like hypothyroidism and acromegaly, craniofacial structural abnormalities, alcohol consumption, cigarette smoking, nasal obstruction, abnormal ventilatory chemosensitivity, periodic breathing, adenotonsillar hypertrophy and having an increasing number of relatives affected by sleep apnoea.

Obesity

Though obesity is by no means a prerequisite, many patients with SAHS are obese (Guilleminault C et al, 1978). So striking and monstrous was obesity in cases of sleep apnoea available in ancient literature that accurate and vivid descriptions of SAHS were given by historians of that time (Athenaeus). Obesity again was a prominent feature of Charles Dicken's description of sleep apnoea in The Pickwick Papers.

Approximately half of the SAHS patients weigh more than 30% of their ideal body weight. Between one half and one third of patients are within 30% of ideal body weight and around 20% of patients within 15% of ideal body weight (Douglas NJ, 1991). Another earlier study found that 85% of the patients had a body mass index of over 30 kg/m^2 (Whyte KF et al, 1989). However, this percentage is

falling progressively with greater recognition that SAHS also occurs in non obese.

Not only does obesity predispose to sleep apnoea (Burwell CS et al, 1956, Seiker HO et al, 1955) but weight loss results in improvement in upper airway obstruction (Harman EM et al, 1982, Brownman CP et al, 1984, Smith PL et al, 1985, Rubinstein I et al, 1988, Suratt PM et al, 1987). All anthropometric indices of obesity whether generalised as reflected by body mass index, truncal as reflected by waist circumference or neck fat as reflected by neck circumference are significantly higher in patients requiring higher CPAP pressures. The pressure required to abolish apnoeas is related to obesity and severity of sleep apnoea (Engleman HM et al, 1994b, Miljeteiz H et al, 1993).

Regional adiposity may also be important in the genesis of sleep apnoea. SAHS patients have thicker necks than non apnoeic snoring controls with external neck circumference, body mass index, age and internal neck circumference accounting for 39% of the variability in the apnoea/hypopnoea frequency (Katz I et al, 1990).

Magnetic resonance imaging has shown that more fat is present in those areas surrounding the collapsible segments of pharynx in patients with SAHS compared to equally obese control subjects without SAHS (Horner RL et al, 1989). They found large deposits of fat posterolateral to the oropharyngeal airspace at the level

of the soft palate in patients with SAHS. Fat deposits were also found in the soft palate and streaking the tongue in these patients. Another study demonstrated that adipose tissue is deposited adjacent to the pharyngeal airway in patients with SAHS and that the volume of this tissue is related to the presence and degree of obstructive sleep apnoea (Shelton KE et al, 1993). Furthermore, they found that the pharyngeal adipose tissue volume did not correlate with the body mass index indicating that the volume of parapharyngeal adipose tissue is not dependent only on the degree of obesity. In a resection study, more adipose tissue has been observed in surgically removed uvulas from patients with SAHS than in uvulas from non-obese subjects obtained at autopsy (Stauffer JL et al, 1989).

Obesity may cause upper airway obstruction by multiple mechanisms. Obesity may narrow the neck by mass loading (Koenig JS et al, 1988, Katz I et al, 1990). This mass loading of the neck may stress the remaining muscle tone during sleep and further contribute to occlusion during sleep (Katz I et al, 1990).

Another mechanism of upper airway collapse could be parapharyngeal adipose tissue compressing the upper airway. This would explain why sleep apnoea develops when subjects gain weight and improves when they lose weight. The location of adipose tissue lateral to the airway could also explain why the airway has been

observed to collapse laterally when observed endoscopically. Presumably pharyngeal airway that has been narrowed from lateral encroachment of tissue is more likely to collapse during sleep , when the tongue moves posteriorly, than the airway that has not been narrowed laterally (Shelton KE et al, 1993).

A third mechanism of upper airway collapse due to adiposity is the increase in pharyngeal compliance promoting complete occlusion during sleep. Fatty infiltrates in the muscles may directly interfere with upper airway muscle function (Katz I et al, 1990, Horner RL et al, 1989) or may change the intrinsic elastic properties of the pharyngeal wall and surrounding structure (Oslen LG et al, 1988). However, the increase in pharyngeal compliance due to fat is disputed (Brown IG et al, 1985).

Lastly, obesity has been shown to cause greater reduction in pharyngeal size in SAHS patients as compared to controls as lung volume is reduced (Hoffstein V et al, 1984). Thus, in suscepitible persons obesity may predispose to upper airway occlusion by reducing upper airway size indirectly, secondary to a decrease in lung volume, rather than directly narrowing the airway aperture. This may also in part explain the improvement in sleep apnoea by CPAP or weight reduction by an increase in FRC associated with these treatment modalities.

Sex

Clinically, SAHS is recognised more in males than females. In one series men accounted for 88% of patients (Guilleminault C et al, 1988b). Two other series found that over 80% of the patients were men (Whyte KF et al, 1989, Guilleminault C et al, 1978a). Likewise snoring, which is a prerequisite for obstructive sleep apnoea, exhibits a male preponderance as 25% of men and 15% of women were found to be habitual snorers in one epidemiological survey (Lugaresi E et al, 1980). In a survey conducted among married couples 86% of the husbands were considered habitual snorers by their wives and 57% of wives were considered so by their husbands (Norton PG et al, 1985).

Although underreporting of symptoms of abnormal breathing during sleep by females has been suggested (Redline S et al, 1994) the sex differences may in part be explained by the effects of testosterone upon ventilation and chemosensitivity (White DP et al, 1985a). SAHS has been induced by testosterone administration both in hypogonadal males (Schneider BK et al, 1986) and females (Johnson MW et al, 1984). Testosterone may promote fat deposition in the neck thereby narrowing the upper airway (Douglas NJ, 1991). Another proposed mechanism of testosterone induced SAHS is an increase in upper airway collapsibility during sleep (Cistulli PA et al, 1994). In another study, women were found to have less severe

SAHS than their male counterparts despite having a slightly greater degree of morbid obesity. These investigators believe that this difference in severity could possibly be due to sex differences in body fat distribution and the female propensity towards lower body adiposity with less fat deposition around the pharynx (Millman RP et al, 1993).

Another possible explanation of the male preponderance of SAHS could be gender related differences in size and mechanical properties of the pharynx. Though men have larger pharynxes than women, men have a larger change in pharyngeal area with changing lung volume. Thus larger pharynxes in men may be more than offset by a greater change in pharyngeal size with changing lung volume contributing to the greater incidence of SAHS in men (Brooks LE et al, 1992).

Age

Chronic snoring is frequent with ageing (Mondini S et al, 1983). The prevelance of snoring is relatively low among young people but increases significantly in both sexes after the age of 35 (Lugaresi E et al, 1980).

Although SAHS occurs in all age groups, most patients present in middle age (Ancoli-Isreal S, 1989) and the incidence of obstructive sleep apnoea increases after the age of 40 (Clark GT et al, 1993). A recent study found the prevelance of sleep disordered breathing at apnoea

hypopnoea scores of >5, >10 and >15 to be significantly higher in men aged between 40-49 years than among those 30-39 years old. Apnoea hypopnoea scores of 5 or higher were more prevelant in women in the age group 50-60 years than among younger women.

Endocrine abnormalities

Endocrine disorders like hypothyroidism predispose to snoring and obstructive apnoeas (Orr WC et al, 1981, Rajagobal KR et al, 1984) probably by inducing myxoedematous structural changes in the upper airways and altered muscle contractility. Acromegaly predisposes to sleep apnoea (Perks WH et al, 1980a, Mezon BJ et al, 1980) as it is also associated with macroglossia, thickening of the pharyngeal mucosa and changes in the facial cartilaginous or bony architecture (Flecther EC et al, 1986). In addition, patients with active acromegaly have been demonstrated to have increased ventilatory responsiveness to hypercapnia contributing to central apnoeas (Grunstein RR et al, 1994). Although in myxoedematous patients sleep apnoea is usually reversible following restoration of euthyroid state with thyroxine (Rajagobal KR et al, 1984), this may not always be the case (Grunstein RR et al, 1986).

Craniofacial skeletal abnormalities

Retrognathia and micrognathia (Tammeling GJ et al, 1972, Coccagna G et al, 1976, Conway WA et al, 1977) are rare

but potentially surgically correctable facial bony abnormalities that predispose to sleep apnoea. Mandibular retrognathism has been demonstrated in 16% (De Berry-Boroweicki B et al, 1988) to 60% (Riley R et al, 1983) of cases with SAHS. This abnormal skeletal pattern, by reducing the posterior air space, reduces the resting airway dimensions behind the tongue and predisposes to upper airway obstruction during sleep. Moreover, the number of apnoeas has been shown to correlate with the total posterior displacement of the mandible (Rivlin J et al, 1984). Mandibular osteostomy with advancement results in improvement in sleep apnoea in cases with overt retrognathia (Kuo PC et al, 1979, Bear SE et al, 1980).

The hyoid bone is frequently abnormally low in SAHS patients as indicated by an increased mandibular plane to hyoid distance and gonion-gnathion-hyoid angle. Guilleminault C et al, 1984b found a low hyoid in 25 out of 30 SAHS patients and in 4 of the 6 patients who did not improve after palatopharynagoplasty and mandibular osteotomy. Riley et al, 1983, found an inferiorly placed hyoid in SAHS patients and demonstrated that those patients who did not improve after palatopharyngoplasty had a low hyoid placement and smaller posterior airspace than the ones who improved with surgery (Riley R et al, 1985). An abnormally low position of hyoid in SAHS patients has also been found by others (Jamieson A et al, 1986, Stretzow VV et al, 1988, De Berry-Borowiecski et

al, 1988, Lyberg T et al, 1989, Zucconi M et al, 1992).

A lower than normal hyoid placement relocates the tongue backwards in the hypopharynx and narrows the retroglossal airway. Combining inferior sagittal osteotomy with hyoid myotomy and suspension has been advocated as the surgical procedure to widen the hypopharynx (Riley R et al, 1986a). Retroposition of maxilla in patients with SAHS has also been demonstrated by numerous investigators. In a sample of 25 adult male SAHS patients, Lowe AA et al, 1986, found posteriorly positioned maxilla in addition to other craniofacial abnormalities. Stretzow VV et al, 1988, demonstrated a short maxilla in 90 SAHS patients. De Berry-Borowiecski et al, 1988, demonstrated retroposed maxillae in 30 adult patients with SAHS. A posteriorly placed maxilla narrows the pharynx behind it and places the soft palate closer to the posterior pharyngeal wall thereby narrowing the passage between nasopharyngeal and oropharyngeal airway. A combined maxillomandibular and hyoid advancement (Riley R et al, 1986b) enlarges the pharynx at all levels and has been advocated as treatment for selected SAHS patients.

In addition to these skeletal discrepancies, soft tissue abnormalities like enlarged tongue, longer soft palates and wider uvulae in patients with SAHS have been reported by many workers (Riley R et al, 1983, Riley R et al, 1985, Lowe AA et al, 1986, De Berry-Borowieski B et al, 1988, Stretzow VV et al, 1988, Lyberg T et al, 1989,

Stauffer JL et al, 1989).

Alcohol consumption

Alcohol can induce both snoring and obstructive apnoeas. Alcohol acts by inducing peripheral vasodilation and consequently nasal mucosal swelling (May M et al, 1973, Robinson RW et al, 1985) by a depressant effect on the respiratory centres in the medulla and by reducing upper airway dilating muscle tone.

In many normal people, ingestion of a small amount of alcohol at bedtime increases the apnoea frequency (Taasan VC et al, 1981a). Older subjects are more vulnerable to this effect of alcohol while both premenopausal as well as post menopausal women seem to be relatively resistant to the development of obstructive apnoeas after a modest amount of bedtime alcohol (Block AJ, 1984, Block AJ et al, 1985). However, habitual snorers may develop prolonged apnoeas after alcohol ingestion (Issa FG et al, 1982). This tendency of the upper airway to obstruct is more in the first 1-2 hours of sleep when the blood alcohol concentrations are highest (Issa FG et al, 1982, Scrima L et al, 1982).

Alcohol seems to have a selective depressant action on the activity of upper airway dilator muscles and this has been demonstrated for genioglossal activity both in animals (Bonora M et al, 1984) and in human subjects (Krol RC et al, 1984). Alcohol seems to depress the

brainstem reticular activating system with more profound effects on the neural mechanisms serving genioglossus and perhaps other upper airway muscles than for those serving the muscles of the respiratory pump. This effect of alcohol on upper airway muscle tone is less pronounced in women (Block AJ, 1984, Block AJ et al, 1985). Pharyngeal inspiratory airflow resistance has been shown to increase during the first hour after alcohol intake (Robinson RW et al, 1985) and less negative intrapleural pressures are required to collapse the upper airway after alcohol intake (Issa FG et al, 1984). Heavy snorers and SAHS patients who have preexistent anatomically narrowed airways (Harponik EF et al, 1983) or defective upper airway muscle function (Issa FG et al, 1984) are more susceptible to alcohol and abstinence from alcohol before bedtime is an important part of therapy.

The long term effects of alcohol on SAHS are less clear cut. Abstinent alcoholics have been reported to have an increased frequency of apnoeas and hypopnoeas (Tan ETH et al, 1985). A significant but weak correlation between alcohol consumption and the frequency of nocturnal oxygen desaturation has also been shown in a population study (Stradling JR et al, 1991a). However, like another (Kauffmann F et al,1989) this study did not find any significant correlation between alcohol consumption and history of snoring. Similarly, another recent study found that patients with SAHS do not have a higher current or lifetime alcohol consumption than controls

(Jalleh R et al, 1992). Thus although acute alcohol ingestion increases apnoea frequency in predisposed individuals, patients with SAHS do not drink excessively.

Nasal obstruction

Nasal obstruction is increasingly recognised as a cause of disturbed breathing during sleep, including apnoeas, hypopnoeas and arterial oxygen desaturation. This holds true both for naturally occuring partial nasal obstruction (McNicholas WT et al, 1982) as well as for induced total nasal occlusion (Zwillich CW et al, 1981). Deviated nasal septum has been reported to cause the syndrome, with surgical correction reversing the SAHS (Olsen KD et al, 1981). Posterior nasal packing increases the number of apnoeas during sleep and has been associated with unexpected sudden death during sleep (Taasan VJ et al, 1981b).

Several reasons have been suggested to explain this association of nasal obstruction with sleep apnoea. The first is the effect on central respiratory drive of breathing via the nasal route. The available data on this issue is conflicting (Widdicombe JG, 1986). Several human (McBride B et al, 1981, Douglas NJ et al, 1983) and animal studies (Fisher JT et al, 1985, Mortola JP et al, 1988) report a depressant effect of nasal airflow on respiration. Other studies, some directly measuring ventilation during conditions of altered nasal airflow (McNicholas WT et al, 1993) and others indirectly by

finding increase in apnoeas after nasal anaesthesia have supported a stimulant effect of nasal airflow on breathing in adult human subjects during sleep (White DP et al, 1985b, McNicholas WT et al, 1987). Further evidence of a stimulant effect of nasal airflow comes from another study which reported an increase in genioglossal and alae nasi EMG activity in awake humans breathing through the nose, an effect which could be blocked by nasal anaesthesia (Basner RC et al, 1989).

A second explanation lies in the observation that nasal route of breathing has a higher airflow resistance than does the oral route (Proctor DF, 1977, Cole P, 1988, Tanaka Y et al, 1988). With reduced nasal patency and ineffect increased nasal resistance, a greater inspiratory force is required to breathe. This yields higher negative intrapharyngeal pressures resulting in partial upper airway collapse. With the relaxation of upper airway dilator muscle activity during sleep, this high negative intrapharyngeal pressure could well produce complete pharyngeal obstruction.

Finally, it has now been documented that nasal obstruction can effect breathing pattern during sleep with central apnoeas being a commonly encountered events (Zwillich CW et al, 1981).

Adenotonsillar enlargement

Upper airway obstruction is a well known cause of sleep

disruption in toddlers and school children and in most cases is caused by adenotonsillar enlargement (Carroll Jl et al, 1992, Guilleminault C et al, 1981a, Van Someran VH et al, 1990, Stradling JR et al, 1990b, Mangar D et al, 1977, Orr WC et al, 1981b, Richardson MA et al, 1980). Enlarged tonsils and adenoids are very common and result in obstructive sleep apnoea in 0.7-1.3% of 4-5 years olds (Ali NJ et al, 1993). Likewise there are reports of SAHS in patients with upper airway tumours (Zorick F et al, 1980). SAHS has also been described in children with sickle cell disease, possibly due to an increased prevelance of adenotonsillar hypertrophy in this age group (Samuels MP et al, 1992). Although serious consequences are rare, pulmonary hypertension has been described with severe tonsillar hypertrophy. Most cases of SAHS with this underlying cause can be dealt successfully by adenotonsillectomy (Guilleminault C et al, 1983, Eliaschar I et al, 1980).

Smoking

Smoking has been shown to increase the likelihood of snoring (Bloom JW et al, 1988). The prevelance of snoring in children has also been found to be higher in smoking households thereby emphasising the role of passive smoking (Corbo GM et al, 1989). Smoking may induce upper airway hyperaemia and congestion and increase upper airway resistance thereby predisposing the airway to collapse.

Periodic breathing and ventilatory chemosensitivity abnormalities

Periodic breathing is often seen in association with congestive heart failure (Harrison TR et al, 1934), exposure to high altitude (Lahiri S et al, 1983), neurological disease (Brown HW et al, 1961) and idiopathic central sleep apnoea associated with hypocapnia (Bradley TD et al, 1986b, Bradley TD et al, 1992, Naughton M et al, 1993). Periodic breathing during sleep in patients with heart failure may cause symptoms of sleep apnoea (Takasaki Y et al, 1989) and induce both central and obstructive apnoeas (Alex CG et al, 1986, Dowdell WT et al, 1990).

Though during wakefulness ventilation is controlled both by metabolic as well as by behavioural systems, during NREM sleep it is controlled almost solely by the metabolic control system with ventilation being tightly linked to afferent inputs from chemoreceptors and intrapulmonary vagal receptors (Sullivan C et al, 1978).

Several mechanisms may explain the genesis of periodic breathing in heart failure. Prolonged circulation time causes time delays in the recognition of arterial blood gas tensions within the lungs by chemoreceptors (Khoo MCK et al, 1982, Guyton AC et al, 1956) and may result in or more probably prolong periodic breathing cycle length (Khoo MCK et al, 1982). Likewise, reduction in lung volumes may fail to dampen oscillations in arterial

blood gases due to reduced O2 and CO2 stores in the lungs (Khoo MCK et al, 1982, Cherniack NS et al, 1986). The most probable mechanism, however, seems to be hypocapnia induced by hyperventilation (Naughton M et al, 1993, Dowell AR et al, 1971, Berssenbrugge A et al, 1983) very often mediated by the stimulation of pulmonary irritant and juxtacapillary receptors due to pulmonary congestion (Churchill ED et al, 1929, Sackner MA et al, 1991, Bradley TD et al, 1992).

The onset of NREM sleep is characterised by a withdrawal of the wakefulness drive to breathe with an increase in the ventilatory threshold for paCO2 (Bradley TD et al, 1992). Chemical drive remains the sole ventilatory stimulus. If paCO2 is below normal at the onset of sleep, the difference between this value and the paCO2 which will stimulate ventilation is exaggerated so that central apnoeas occur until the paCO2 rises to the ventilatory threshold. When the paCO2 is near the apnoeic threshold, the slight perturbations caused by an arousal are sufficient to reduce the paCO2 to below the critical level necessary to precipitate a central apnoea (Xie A et al, 1994, Khoo MCK et al, 1991, Berssenbrugge A et al, 1983). Thus such apnoeas are the consequence and not the cause of arousals. The greater apnoea hypopnoea frequency in stage 1 and 2 of NREM sleep than in slow wave sleep is explained by the lower paCO2 and increased arousability in stages 1 and 2 with a resultant tendency to hyperventilate. Once slow wave

sleep is reached, ventilation becomes rhythmic under metabolic control. As the control of breathing during REM sleep is independent of chemical and metabolic stimuli and arousability to chemical stimuli blunted (Douglas NJ et al, 1982a, Douglas NJ et al, 1982b), central apnoea/hypopnoea frequency in REM may be less than that in NREM sleep.

Genetics- A common denominator for some of the risk factors for SAHS

Many of the risk factors described above are themselves thought to be genetically determined in a major part. This is true for obesity (Stunkard AJ et al, 1986a, Stunkard AJ et al, 1986b), craniofacial structure (Lundstorm A et al, 1984), ventilatory control abnormalities (Kawakami Y et al, 1984, Fleetham JA et al, 1984) and alcohol consumption (Schuckit MA, 1985, Goodwin DW, 1987). In reports of single families, some of the inherited risk factors have been shown to cause familial sleep apnoea. These risk factors include abnormal craniofacial anatomy (Guilleminault C et al, 1986b), defective ventilatory control (El Bayadi S et al, 1990) metabolic diseases like mucopolysaccharidosis (Perks WH et al, 1980b) and defective motor activity of the tongue during sleep (Strolh KP et al, 1978). However despite this sporadic data, the relationship of familial sleep apnoea to the inheritance/familial aggregation of these specific risk factors still remains unclear.

Inherited diseases associated with SAHS

SAHS has been described with heriditary ataxias like autosomal dominant olivopontocerebellar degeneration (Chokroverty S et al, 1984). SAHS has also been reported with other autosomal dominant disorders like myotonica dystrophica (Guilleminault C et al, 1978b) and achondroplasia (Fremion AS et al, 1984) as well as with autosomal recessive conditions like mucopolysaccharidosis (Perks WH et al, 1980b). There are also reported associations of SAHS with chromosomal disorders like Down's syndrome (Stebbens VA et al, 1991) and with other diseases having a genetically determined predisposition like multiple sclerosis (Manon-Espaillat R et al, 1986).

Family reports on the inheritance of SAHS

The first well documented report of obstructive sleep apnoea in family members was by Strohl KP et al in 1978. They described two sons (body mass index 47.4 kg/m^2 and 25.4 kg/m^2) and their father (body mass index unknown) with severe hypersomnolence and obstructive sleep apnoea. A third son (body mass index 28.3 kg/m^2), a snorer but otherwise asymptomatic, was shown to have upper airway obstruction during sleep. Genioglossal EMG recordings in two symptomatic sons showed loss of tonic activity in early stages of NREM sleep when upper airway obstruction occurred. The asymptomatic son showed loss of tonic activity during REM sleep when sleep apnoeas occurred. Two sudden deaths occurred in this family. A 30 years old

brother (body mass index unknown), also a snorer, died while asleep and the death was attributed to other reasons though no autopsy was performed. A 4 month old daughter of the asymptomatic son died of presumed sudden infant death syndrome. Ventilatory responses to CO2 were normal in all family members tested. These authors concluded that the familial factors predisposing to SAHS may be a genetic abnormality of the motor activity of tongue during sleep.

In the same year, another study undertaken at the Gainesville Veterans Administration Hospital, Florida, and described by J Elliot provided further evidence that some cases of SAHS have a heriditary factor. This study of a Georgia family described episodic apnoea, hypoventilation and oxygen desaturation in a 39 years old male patient displaying classical sleep apnoea as well as in his 9 year old son and 32 year old brother. Despite adenotonsillectomy, the 9 year old son continued to have episodic sleep apnoea.

In 1980b, Perks WH et al described in two brothers aged 18 and 25 years and having Scheie's syndrome- a mucopolysaccharidosis characterised by short stature, micrognathia, corneal clouding, hepatosplenomegaly, raised urinary mucopolysaccharides and undetectable levels of alpha-L-iduronidase assayed in cultured fibroblasts. Both the brothers had excessive daytime sleepiness, noisy breathing during sleep and an apnoea

index of 59 and 35 respectively. They believed that in this family the familial predisposing factor for SAHS was mucopolosaccharidosis related micrognathia and macroglossia.

In 1982 Walsh JT et al described sleep apnoea in combination with open angle glaucoma in 5 members of 2 generations of a family. Three surviving members with heavy snoring and glaucoma and a fourth with heavy snoring alone had confirmed sleep apnoea. Severity of glaucoma, its resistance to surgery and medication, correlated with a greater number and duration of apnoeas. Moreover, in contrast to the usual occurence of higher intraocular pressures later in the day in the garden variety of glaucoma, these patients with SAHS and glaucoma exhibited maximum intraocular pressures in the morning. These observations lead these investigators to conclude that the sleep apnoea may have resulted in a morning rise of intraocular pressure in these patients. They postulated SAHS related changes in venous pressure and fluctuations in intrathoracic pressure were responsible for the increase in intraocular pressures. They did concede however, that sleep apnoea and glaucoma could be independently inherited without one having an influence on the other.

In 1986b Guilleminault C et al reported the relationship between sudden infant death syndrome and adult obstructive sleep apnoea in 5 families. Six index

infants from these 5 families had a near miss sudden infant death syndrome event between 3 and 12 weeks of age and had polygraphically documented apnoeas during sleep. Four of their siblings had died of SIDS. The 6 index infants, their 4 living siblings, 10 parents and 8 grandparents underwent sleep studies. All the adults and 3 index infants had cephalometry and 2 index infants underwent volume CT scans while awake and asleep. Several family members of the index infants were shown to have obstructive sleep apnoea while cephalometric X rays showed small upper airways particularly behind the base of the tongue. They concluded that a small posterior air space in these infants and adult family members was the common denominator leading to long obstructive apnoeas which, if sufficiently long, triggered cardiovascular changes that could cause unexpected infant deaths.

In 1988 Manon-Espaillat R et al described a familial disorder consisting of sleep apnoea, anosmia, colour blindness, complex partial seizures and cognitive dysfunction. Though cognitive dysfunction and recurrent hippocampal hypoxia with neuronal degeneration and resultant seizures may be consequences of sleep apnoea these authors postulated that the association of sleep apnoea, anosmia, complex partial seizures and cognitive dysfunction are the manifestations of a mutant gene. This is because of the low probability of all these independent afflictions occuring in a single individual or family. The phenotypic expression of this syndrome

suggests an autosomal dominant inheritance with incomplete penetrance.

In 1990 El Bayadi S et al studied 10 members of one family with 3 generations of subjects with SAHS. They reported questionnaire data, sleep study data and ventilatory responses to hyperoxic hypercapnia and eucapnic hypoxia in some of these subjects. All 10 members reported habitual snoring or nighttime snorting/gasping while 5 also reported excessive daytime sleepiness. All had an apnoea hypopnoea frequency of greater than 10 per hour slept. They demonstrated markedly diminished ventilatory responses to hypoxia in all 5 subjects studied and diminished response to hypercapnia in 3 out of 5 subjects studied. In fact in the index subject, ventilation decreased with worsening hypoxia leading them to believe that depressed hypoxic responsiveness may be the major genetic predisposition to the disorder. They also found reduces posterior airspace and increased hyoid to mandibular plane distance in 4 subjects. From the distribution of physiological and anatomical abnormalities in this family, they concluded a genetic basis for SAHS (autosomal dominant) and suggested that the interaction between familial primary ventilatory control abnormalities and familial anatomic risk factors is responsible for the genesis of this syndrome.

The familial clustering of symptoms of SAHS have recently been assessed in a sleep symptom questionnaire based

study (Redline S et al, 1992a). This study described more daytime sleepiness and apnoeas in relatives of patients with SAHS. A progressive increase in risk of reporting these symptoms was associated with increasing numbers of relatives reporting the same symptom. However, sleep studies were not performed in this study and the possibility of relatives being more aware of the symptoms could not be excluded.

A preliminary report of a genetic epidemiological study of risk factors for sleep apnoea has described increased abnormal breathing during sleep in the families of patients with SAHS. Familial factors including those associated with race and craniofacial anatomy were found to be important determinants of sleep apnoea in younger subjects (Redline S et al, 1992b).

Further support to the genetic basis of SAHS has been lended by HLA studies in 32 Japanese patients with this syndrome (Yoshizawa T et al, 1993). The frequency of HLA-A2 antigen was markedly increased in SAHS patients compared with normal controls (81.3% vs 40.6%) and compared with the Japanese population (40.7%). HLA-B39 was found more frequently in SAHS patients than in Japanese population but not in the controls. No significant deviations were seen in the prevelance of HLA-C and DR antigens between patients and controls. The authors concluded that genetics is important in the development of SAHS.

CHAPTER 3

PILOT STUDY ON THE INHERITANCE OF SAHS

PILOT STUDY ON THE INHERITANCE OF SLEEP APNOEA/HYPOPNOEA SYNDROME

INTRODUCTION

The aetiology of SAHS in many patients is unclear. As explained in the previous chapter familial SAHS has been described in many reports of single families. However, these reports are confounded by the familial nature of obesity (Stunkard AJ et al, 1986a & b). Therefore a pilot study was performed to investigate the hypothesis that SAHS may be inherited. As one did not wish to restudy the familial nature of obesity (Stunkard AJ et al, 1986a & b), index cases who were relatively non-obese were selected.

METHODS

Twenty consecutive new patients with SAHS took part in the study. All these patients had more than 15 apnoeas + hypopnoeas per hour of sleep in association with at least two of the major symptoms of SAHS (Gould GA et al, 1988). All had a body mass index (BMI) of less than 30 kg/m^2. None had clinical evidence of gross retrognathia, hypothyroidism or acromegaly.

These 20 patients (17 male) had a mean (SD) age of 55 (10) years, BMI 27.3 (1.6) kg/m^2, collar size 41.1 (1.7) cm, apnoea hypopnoea index 40 (20) per hour of sleep and arousals 19 (8) per hour of sleep. Arousals were defined as a return to alpha or theta EEG rhythm for at least 1.5

seconds with a concomitant increase in EMG tone (Cheshire K et al, 1992) Each of these index patients was asked to provide details of all first degree relatives aged 18-75 years who were then approached to participate in the study. All the relatives were sent a sleep symptom questionnaire and those living within 150 miles of Edinburgh were invited for an overnight full polysomnography at the Scottish National Sleep Laboratory. All the relatives attending for overnight polysomnography had lateral cephalometry performed as well. Local ethics committee approval was obtained for the study.

Sleep symptom questionnaire

The questionnaire included queries on the date of birth, collar size, height, weight, alcohol consumption and the presence or absence of sleep symptoms. Smoking, drug, family and medical histories were also recorded. Bed partners where available were asked about the subject's behaviour during sleep.

Loud snoring was considered present if the bed partner reported habitual snoring of sufficient intensity to disturb others.

Nocturnal apnoeas were considered present if the bed partner reported witnessing episodes of cessation of breathing, gasping, snorting or struggling for air while the subjects were asleep.

Excessive daytime sleepiness was considered present if the subjects averaged two naps per day when not in bed.

Sleeping against will was considered present if the subjects reported falling asleep in embarrasing or dangerous circumstances, for example when driving.

Current alcohol consumption was calculated in units of alcohol per week.

Current cigarette smoking was judged if the subjects reported smoking at least one cigarette a day during the previous month.

Overnight polysomnography

The sleep study included recording airflow at the mouth and nostrils by thermocouples, thoracoabdominal movement by inductance plethysmogram, ear lobe oxygen saturation by Ohmeda Biox 3700 oximeter and an electroencephalogram, electrooculogram, submental and tibial electromyogram. All the data was recorded on a 16 channel polygraph (Specialised Laboratory Equipment). Sleep (Rechtschaffen A et al, 1968) and breathing pattern (Douglas NJ et al, 1992) were manually scored by standard criteriae.

The parameters calculated from the sleep study were-

Time in bed (TIB): Time in minutes from 'lights out' at the start of sleep study to the end of study.

Sleep onset latency (SOL): Time in minutes from 'lights

out' to the 1st epoch of stage 2 of NREM sleep (sleep onset).

REM onset latency (REM LAT): Time in minutes from 1st epoch of stage 2 NREM sleep (sleep onset) to the 1st epoch of first cycle of REM sleep (REM onset).

Sleep period time (SPT): Time in minutes from sleep onset till the end of sleep study. This includes time asleep and awake.

Total sleep time (TST): That part of the sleep period time in minutes when the subject was actually asleep.

Sleep efficiency index (SEI): The ratio of total sleep time to time in bed and expressed as percentage.

Arousal: A return to alpha or theta EEG frequency for at least 1.5 seconds with a rise of chin EMG howsoever brief (Cheshire K et al, 1992).

Apnoea: An episode during sleep of complete cessation of flow at nose and mouth for at least 10 seconds (Guilleminault C et al, 1978a).

Hypopnoea: An episode during sleep of over 50% reduction of thoracoabdominal movement for at least 10 seconds when compared to the peak amplitude obtained over a 10 second period that had occured in the last 2 minutes (Gould GA et al, 1988).

Arousals/hour: Number of arousals per hour of sleep.

This is obtained by dividing the total number of arousals throughout the night by total sleep time.

AHI: Number of apnoeas plus hypopnoeas per hour of sleep. This is obtained by dividing the total number of apnoeas plus hypopnoeas occuring throughout the night by total sleep time.

Lowest oxygen saturation (Lowest Sao2): From the overnight oximetry tracing.

Cephalometry

Cephalometric roentgenograms were carried out with the subject both seated erect and lying supine while the beam was directed at right angles to the head. For the erect seated position, the subjects gazed forwards with the Frankfurt horizontal plane parallel to the floor and for the supine film, upwards. The head was held in natural posture for both these positions (Moorvees CFA et al, 1958, Bean J et al, 1970, Halperin SL et al, 1959) and the head position was maintained by the use of a cephalometric head holder. The subjects kept their mouths closed with their normal resting occlusion. The lips were together, tongue relaxed on the floor of the mouth and the subjects did not swallow during the exposures. Films were taken with the subjects exhaling slowly from a deep breath. The X-ray cone was positioned exactly 5 feet from the radiographic film which was placed against the left side of the face. Exposure

windows included the full face superiorly from the supraorbital ridges down to the bottom of the laryngeal cartilages including the hyoid bone and base of tongue.

Skeletal discrepancies were evaluated with reference to the cranial base, which is a plane drawn through sella to the nasion in natural head position (Riley R et al, 1983).

The following cephalometric landmarks were identified on both erect and supine films.

Point A: Subspinale-the deepest point on the premaxillary contour between anterior nasal spine and upper central incisor.

Point B: Supramentale-the deepest point on the anterior mandibular contour between gnathion and lower central incisor.

ANS: Anterior Nasal Spine-anterior most point on the nasal spine.

PNS: Posterior Nasal Spine-tip of the spine of the palatine bone of hard palate.

Ar: Articulare-the intersection of a line along the posterior border of mandible and the inferior border of the basilar occipital bone.

Aat: Anterior tubercle of atlas.

Go: Gonion-the point defining angle of mandible (the

mandibular plane and ramus plane form the mandibular angle.

Gn: Gnathion-the most outward and elevated point on the mandibular symphysis.

H: Hyoid bone-the most anterosuperior point on the body of hyoid bone.

N: Nasion-the most anterior point of the nasofrontal suture.

S: Midpoint of sella tursica.

PhW: Posterior pharyngeal wall-soft tissue landmark defining the nasal, oral and laryngeal limits of the pharyngeal wall.

MP: Mandibular Plane-constructed from gonion to gnathion.

Ba: Basion-midpoint of the anterior border of the foramen maganum.

TB: Tongue Base-posteriormost point on the posterior tongue profile.

UP: Uvula Protrusion-greatest posterior convexity on the soft palate.

UT: Uvula Tip-apex of the soft palate, ie lowest point on the soft palate.

Point X: Intersection of lines joining S-Ba and Gn-Go.

The following distances in millimeters and angles in degrees were measured on both erect and supine films.

ANS-PNS: Indicates length of hard palate.

Go-Gn: Measures mandibular body size (small in micrognathia).

S-Go: Measure of mandibular height.

Go-H

H-MP (vertical distance): Measures position of the hyoid bone with respect to the mandibular plane.

H-Ar

Go-PhW: If small, this is indicative of retrognathia.

Go-Ar

UP-PhW: Measure of retropalatal space.

UL: Uvula Length-distance from PNS to UT (length of soft palate).

UW: Uvula Width-at the widest point.

PAS: Posterior Air Space-line drawn through Point B and Go. This line intersects TB and PhW. TB-PhW is the PAS.

UT-PhW

H-PhW (parallel to MP)

PNS-PhW (parallel to Point B-GO)

TB-PhW (parallel to MP)

PNS-Aat: If small, this indicates maxillary retroposition.

Go-X-Ba triangle (area of triangle bound by these points)

Go-Ga-H: This angle indicates the position of hyoid bone.

S-N-A: If small, this angle indicates maxillary retroposition.

S-N-B: If small, this angle indicates mandibular retroposition.

Mandibular angle: Angle formed by the intersection of lines passing through MP and the ramus plane from the gonion angle.

Neck angle: The acute angle created by the intersection of a line drawn through the anterior border of 2nd cervical vertibrae with another line drawn through the anterior border of 4th cervical vertibrae.

N-S-Ba angle: Indicates flexure of the cranial base.

Gn-Go-Aat angle

Gn-Go-Ba angle.

Statistical analyses

Differences between groups were assessed by the unpaired and paried Student's t test or chi square test with appropriate corrections for small numbers and Fisher's exact test as appropriate. Correlations and 95% confidence limits were performed with SPSS-PC.

RESULTS

Subject recruitment

Three of the 20 patients had no eligible first degree relatives. Therefore 17 SAHS patients (15 males) provided relatives for the study. These 17 relative had a mean (SD) age of 53 (10) years, BMI of 27.4 (1.6) kg/m^2, collar size (males only) 41.4 (1.6) cm, apnoea hypopnoea index 41.6 (19.3) per hour of sleep and 18.3 (7.5) arousals per hour of sleep.

These 17 patients had a total of 76 first degree relatives 61 of whom participated in the study by completing the sleep symptom questionnaires.

Fourteen of the 76 relatives lived more than 150 miles from Edinburgh. Six of the remaining 62 relatives (eligible relatives) stated they were too ill to attend for sleep studies. Sixteen of the remaining 56 relatives refused to come to the sleep laboratory for sleep study. Thus 40 eligible relatives (19 males) had overnight sleep studies. Of the 16 eligible relatives who refused sleep

studies, 12 (9 males) returned the questionnaire. Nine out of 14 relatives who lived more than 150 miles from Edinburgh replied to the questionnaire. Therefore, overall 21 (12 males) of the 36 relatives who did not have sleep studies replied to the questionnaire. No questionnaire or sleep study data was available in 15 cases- 6 in the 'too ill' group, 4 in the 'sleep study refused' group and 5 in 'living more than 150 miles away' group. 9 of the 22 relatives who did not attend for sleep studies came from one family.

Thus of a total of 76 relatives-

Group 1. 40 relatives replied to questionnaire and had sleep studies,

Group 2. 12 relatives who refused sleep studies and 9 who lived more than 150 miles from Edinburgh replied to questionnaire alone,

Group 3. Neither questionnaire nor sleep studies data was available in 6 relatives who were too ill to attend for sleep studies, in 4 relatives who refused sleep studies and in 5 relatives who lived more than 150 miles from Edinburgh.

Examining the data for bias due to non participation

The 40 relatives (group 1) with sleep study (and questionnaire) data can be compared with 21 relatives (group 2) on whom only questionnaire data is available.

These 40 relatives (19 male) had a similar sex distribution as the 21 (12 male) who replied only to the questionnaire (p=0.5). The remaining 15 cases (group 3) cannot be included in any comparision analysis as no data whatsoever is available on them.

Prevalance of snoring: 13 of 40 relatives in group 1 reported loud snoring versus 15 out of 21 in group 2, p= 0.002.

Prevalance of excessive daytime sleepiness: 12 of 40 relatives in group 1 had excessive daytime sleepiness versus 4 of 21 in group 2, p= 0.5.

Prevalance of witnessed apnoeas: 5 of 40 relatives in group 1 had witnessed apnoeas versus 2 of 16 in group 2, p= 0.7.

Sleep studies

Ten (9 males) of the 40 relatives had more than 15 apnoeas + hypopnoeas per hour of sleep (affected relatives) while the remaining 30 (10 males) had less than 15 apnoeas + hypopnoeas per hour slept (unaffected relatives). Eight of the 40 relatives had more than five 4% oxygen desaturations per hour.

The affected relatives were older but not more obese than the others. The affected relatives had more frequent arousals from sleep and lower minimal oxygen saturations than the 30 unaffected relatives. There were no other

significant differences in polysomnography results between affected and unaffected relatives.

The polysomnography results in affected and unaffected relatives are summarised in table 3.1.

Table 3.1: Characteristics of relatives with >15 A + H/hour of sleep or <15 A + H/hour of sleep.

	>15 A+H/hr		<15 A+H/hr		P
n	10		30		
Sex	9M, 1F		10M, 20F		0.003*
	Mean	95% CI	Mean	95% CI	
Age(y)	44	26-58	33	19-67	0.03*
BMI-men (kg/m^2)	27	21-33	25	15-35	0.3
Arousals per hr	16	7-45	9	2-22	0.009*
Lowest SaO2(%)	81	71-90	87	69-95	0.02*
TIB(min)	417	365-450	414	336-445	0.9
SOL(min)	18	5-34	26	2-59	0.4
REMLAT (min)	153	26-318	134	65-246	0.6
SPT(min)	393	307-431	382	318-436	0.5
TST(min)	328	239-386	345	201-420	0.3
SEI(%)	79	52-93	85	64-96	0.2

A+H- apnoeas plus hypopnoeas, BMI- body mass index, CI- 95% confidence intervals, * indicates $p<0.05$.
Arousals as per Cheshire K et al, 1992.

Correlation of A + H/hour of sleep with anthropometric measurements

Factors significantly correlated with abnormal breathing during sleep were sex, body mass index (Pearson's $r=0.6$, $p<0.01$) and age (Pearson's $r=0.6$, $p<0.01$) but not collar size (Pearson's $r=0.3$, $p=0.7$). A multiple regression model showed that BMI and age could explain 43% of the variability in the A+H/hour of sleep in all relatives.

Questionnaires

Seven out of 10 affected relatives had current bed partners as compared with 21 of 30 unaffected ($p=0.99$). Eight out of 10 affected relatives were loud snorers compared with 5 of the 30 unaffected ($p=0.0005$). Likewise 5 out of 8 affected relatives reported the presence of witnessed apnoeas compared with none of the 25 unaffected ($p=0.0002$).

Tables 3.2 and 3.3 list other results of sleep symptom questionnaire which were not significantly different between affected and unaffected relatives.

Table 3.2- Subject characteristics of affected and unaffected relatives

Parameter	Aff. Rel	Unaff. Rel	P
Collar size(cm)	41 SEM 1	40 SEM 1	0.5
Alcohol(u/wk)	16 SEM 4	11 SEM 2	0.3
Alcohol at bedtime	3/10	14/30	0.5
Current smokers	2/10	9/30	0.4

SEM-Standard Error of the Mean, u/wk-number of units of alcohol consumed per week.

Table 3.3- Other questionnaire results which did not achieve statistical significance at $p<0.05$.

Parameter	Aff. Rel	Unaff. Rel	P
Excessive daytime sleepiness	2/10	10/30	0.7
Sleeping against will	1/10	0/30	0.3
Restless sleep	2/7	5/21	0.9
Refreshing sleep	5/10	16/30	0.9
Nocturnal choking	1/10	0/30	0.3
Morning headache	0/10	6/30	0.3
Irritability	2/10	4/30	0.7
Nocturia	9/10	20/30	0.2
Decreased libido	1/7	4/30	0.9
Pedal oedema	0/10	5/30	0.3
Recent weight gain	6/10	15/30	0.7
Significant past medical history	8/10	17/30	0.3

Significant past medical history includes history of any nose or throat surgery or of nasal bone fracture in the past.

Cephalometry

Cephalometric measurements were compared between the 10 affected relatives (9 male) and 10 unaffected relatives (9 males) matched by priority for sex, family (possible in 3 cases) and height (Fig 3.1). The measurements which were different in the affected relatives were the gonion-gnathion-hyoid angle (affected 30 SEM 2 degrees, unaffected 21 SEM 1 degrees, $p=0.01$) and uvular width (affected 13 SEM 1 mm, unaffected 10 SEM 1 mm, $p=0.01$).

Tables 3.4 and 3.5 list other cephalometric measurements in the 10 matched affected and unaffected relatives in supine and erect postures. These did not achieve statistical significance at $p<0.05$.

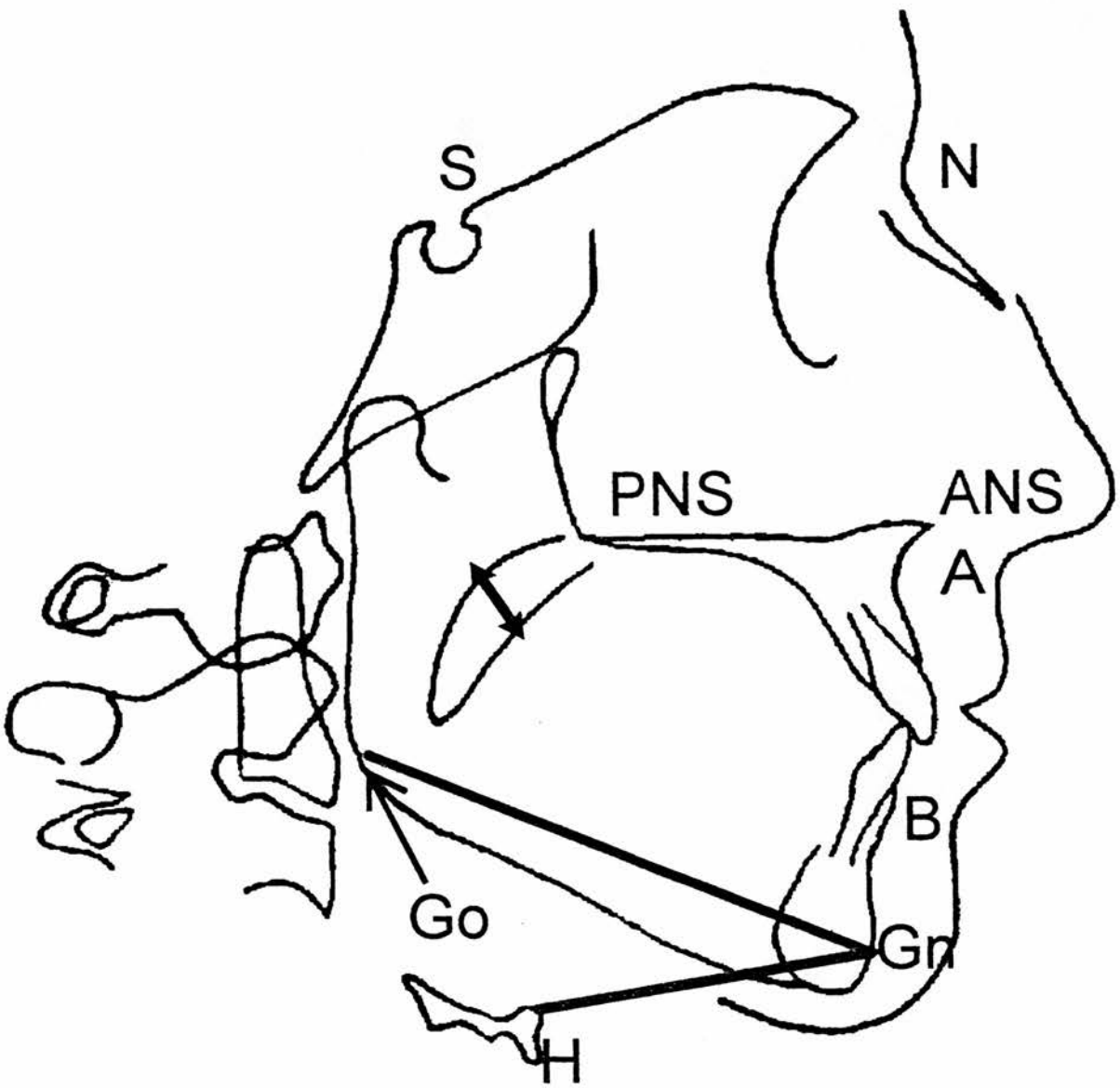

Fig 3,1

Table 3.4- Cephalometric analysis results not reaching statistical significance in 10 matched affected and unaffected relatives in supine posture.

Parameter	Aff. Rel	Unaff. Rel	P
ANS-PNS(mm)	59 SEM 2	58 SEM 2	0.9
Go-Gn(mm)	87 SEM 2	85 SEM 2	0.4
S-Go(mm)	97 SEM 2	97 SEM 3	0.9
GO-H(mm)	45 SEM 3	40 SEM 3	0.2
H-MP(mm)	26 SEM 2	22 SEM 2	0.1
H-Art(mm)	113 SEM 4	103 SEM 4	0.1
Go-PhW(mm)	90 SEM 1	91 SEM 3	0.7
Go-Art(mm)	67 SEM 2	66 SEM 2	0.7
UP-PhW(mm)	6 SEM 1	7 SEM 1	0.4
UL(mm)	52 SEM 2	48 SEM 1	0.2
UW(mm)	14 SEM 1	12 SEM 1	0.1
PAS(mm)	14 SEM 1	15 SEM 2	0.6
UT-PhW(mm)	10 SEM 1	10 SEM 1	0.8
H-PhW(mm)	41 SEM 2	38 SEM 1	0.2
PNS-PhW(mm)	30 SEM 1	32 SEM 1	0.3
TB-PhW(mm)	14 SEM 1	15 SEM 2	0.6
PNS-Aat(mm)	40 SEM 2	41 SEM 1	0.7
Triangle(mm^2)	989 SEM 170	967 SEM 116	0.9
S-N-A(deg)	86 SEM 4	83 SEM 1	0.5
S-N-B(deg)	83 SEM 4	80 SEM 1	0.4
Mandibular angle	126 SEM 3	123 SEM 2	0.4
Neck angle	11 SEM 3	10 SEM 2	0.8
N-S-Ba(deg)	126 SEM 3	129 SEM 2	0.5
Gn-Go-Aat(deg)	128 SEM 4	127 SEM 4	0.9
Gn-Go-Ba(deg)	134 SEM 4	131 SEM 3	0.5

Abbreviations as described in methods section, SEM-Standard Error of Mean.

Table 3.5- Cephalometric analysis results not reaching statistical significance in 10 matched affected and unaffected relatives in erect posture.

Parameter	Aff. Rel	Unaff. Rel	P
ANS-PNS(mm)	59 SEM 2	58 SEM 2	0.9
Go-Gn(mm)	87 SEM 2	85 SEM 2	0.4
S-Go(mm)	96 SEM 2	94 SEM 4	0.7
GO-H(mm)	45 SEM 3	42 SEM 2	0.3
H-MP(mm)	28 SEM 1	23 SEM 2	0.1
H-Art(mm)	111 SEM 3	104 SEM 2	0.08
Go-PhW(mm)	83 SEM 1	86 SEM 3	0.4
Go-Art(mm)	67 SEM 2	65 SEM 2	0.5
UP-PhW(mm)	6 SEM 1	8 SEM 1	0.2
UL(mm)	50 SEM 2	47 SEM 1	0.4
PAS(mm)	12 SEM 1	13 SEM 2	0.7
UT-PhW(mm)	8 SEM 1	10 SEM 1	0.4
H-PhW(mm)	39 SEM 2	36 SEM 1	0.2
PNS-PhW(mm)	28 SEM 1	31 SEM 1	0.09
TB-PhW(mm)	12 SEM 1	12 SEM 2	0.9
PNS-Aat(mm)	37 SEM 2	38 SEM 1	0.6
Triangle(mm^2)	886 SEM 140	1040 SEM 160	0.5
Go-Ga-H(deg)	33 SEM 3	25 SEM 3	0.09
S-N-A(deg)	86 SEM 4	84 SEM 1	0.5
S-N-B(deg)	89 SEM 6	80 SEM 1	0.2
Mandibular angle	126 SEM 3	123 SEM 2	0.4
Neck angle	13 SEM 4	14 SEM 2	0.8
N-S-Ba(deg)	126 SEM 3	129 SEM 2	0.5
Gn-Go-Aat(deg)	125 SEM 4	121 SEM 3	0.5
Gn-Go-Ba(deg)	134 SEM 3	131 SEM 3	0.6

Abbreviations as described in methods section, SEM-Standard Error of Mean.

DISCUSSION

The main conclusions from this pilot study are that 10 of the 40 first degree relatives of non obese patients with SAHS had over 15 apnoeas plus hypopnoeas per hour of sleep. Eight of these 40 relatives had more than five 4% oxygen desaturations per hour.

There was no in house control group in this study. The first comparision is with a group of 33 asymptomatic subjects with a BMI of less than 30 kg/m^2 who were previously studied in the same sleep laboratory. None of these 33 subjects had more than 15 apnoeas plus hypopnoeas per hour of sleep (Gould GA et al, 1988) while 8 of the 35 first order relatives in this uncontrolled study with a BMI of <30 kg/m^2 had more than 15 A+H/hr. This indicates that these relatives had abnormal breathing during sleep ($p<0.005$).

The second comparision is with a population study from Oxford, England on the prevalance of more than five 4% desaturations per hour during sleep (Stradling JR et al, 1991a) in a normal population. In a random study of 893 middle aged British men that study reported 45 men who had more than five 4% desaturations per hour. In this study, using the same oximeter and a similar desaturation algorithm, 8 out of all 40 ($p<0.0001$) or 7 out of 19 male relatives ($p<0.0001$) with more than five 4% desaturations per hour were found.

The recruitment of only 40 out of 62 eligible relatives did not affect these conclusions as the findings in this study of an increased frequency of desaturation remain valid even if one assumes that all the 22 relatives who did not have sleep studies breathed normally during sleep. These relatives still show an increased frequency of desaturation (8/62, present study vs 45/893, Oxford study, $p<0.01$) and irregular breathing (10/62, present study vs 0/33 previous study, $p<0.05$). In addition, the higher prevalance of snoring in the 21 relatives who returned the questionnaire but did not have sleep studies suggests that they would have an even higher frequency of irregular breathing than those relatives studied. Thus, the fact that these 21 relatives were not studied biased against the positive findings of this study.

In the 9 families with 100% coverage, 6/19 relatives (32%) had more than 15 A+H/hr of sleep as compared to 0/33 (Gould GA et al, 1988) in the previous study ($p=0.002$). The frequency of having more than five 4% desaturations per hour was also higher in relatives from the families with full coverage as compared to population data (Stradling JR et al, 1991a) from the Oxford study (5/19 vs 45/893, $p=0.003$).

Despite having only 10 matched pairs of relatives for comparision, this study indicates that cephalometric differences between affected and unaffected relatives are mainly in soft tissues rather than in craniofacial

skeletal architecture. The study does not prove a cause and effect relationship between abnormal breathing during sleep and cephalometric abnormalities. Though a thicker uvula in affected relatives may suggest increased fat deposition or increased muscle tissue as a primary abnormality (Stauffer JL et al, 1989) tissue oedema or inflammatory cell infiltration of the soft palate may be a consequence of vibration induced injury to the uvula (Cohn M et al, 1986). Likewise an increased Go-Gn-H angle in affected relatives may be secondary to abnormal breathing during sleep.

CHAPTER 4

METHODS: CASE CONTROL FAMILY STUDY

METHODS: CASE CONTROL FAMILY STUDY IN PATIENTS WITH SAHS

In the preceding pilot study described, a higher frequency of irregular breathing during sleep was found in relatives of patients with SAHS than in retrospective healthy unmatched controls. Control subjects, matched with relatives, were not studied on a prospective basis. The results obtained on relatives were compared with the available population data and therefore the match was imperfect.

However, despite being flawed, the pilot study strongly suggested familial aggregation of abnormal breathing during sleep. Therefore a case control study was designed to determine whether there is genuinely a familial tendency to SAHS and to identify predisposing risk factors.

Patient recruitment

Over a 2 years period consecutive patients with SAHS attending the Scottish National Sleep Laboratory were recruited for the study. As in the pilot study, all the index patients had more than 15 apnoeas plus hypopnoeas per hour of sleep in association with at least 2 major symptoms of SAHS. As obesity, a risk factor for SAHS, is itself familial (Stunkard AJ et al, 1986a & b) SAHS patients with a body mass index of over 30 kg/m^2 were excluded from the study.

The other exclusion criteriae for the patients were gross retrognathia, hypothyroidism or acromegaly. SAHS patients with neuromuscular diseases, congestive cardiac failure and those on treatment with corticosteroids, tricyclic antidepressants, hypnotic sedatives and beta adrenalgic blockers were also excluded from the study. None of the index patients used in this study were included in the pilot study.

Recruiting relatives

Each SAHS patient enroled in the study was asked to give details of all first degree relatives aged 15-75. The relatives were then contacted individually by post or sometimes personally in their homes and requested to participate in the study. In order to obtain as complete a family cover as possible, all first degree relatives irrespective of their geographical area of residence were approached. This amounted to contacting many relatives living all over Britain as well as overseas.

Finding controls

The control subjects were subsequently recruited from a local general practitioner register and were matched on a one to one basis for sex, weight, height and age in that order with each of the relatives studied. All four of these measurements were available in approximately 5% of all control case records surveyed manually in the general practitioner's surgery. In the first instance, all

control subjects were contacted by a letter from their own doctor. Those showing a willingness to participate were then seen in their homes for detailed explanations.

All the relatives and controls gave written informed consent for participation and local ethics committee approval was obtained for the study. All were posted sleep symptom questionnaire and requested to attend the sleep laboratory for overnight polysomnography and upper airway measurements by acoustic reflectance and lateral cephalometry. The whole procedure in the hospital took around 14 hours.

Questionnaires

The same questionnaires that were used in the pilot study were completed by the relatives and their matched controls. The questionnaire included similar questions and the various sleep symptoms were defined as in the pilot study.

Polysomnography

The relatives and controls each underwent one night sleep study as described in the pilot study. The data were recorded on paper using a 20 second sleep epoch. Sleep (Rechtschaffen A et al, 1968) and breathing (Douglas NJ et al, 1992) were manually scored using standard criteriae as in pilot study.

For each subject, the actual time spent awake in bed and

in each of the sleep stages, including movement time, were measured. Light sleep was defined as total time spent in stages 1 and 2 combined while slow wave sleep (deep sleep) as the total time spent in stages 3 and 4 combined of NREM sleep. The time spent in each stage of sleep, light sleep and slow wave sleep was also expressed in terms of percentage of sleep period time.

Arousal was defined as a return to EEG alpha or theta rhythm of at least 3 seconds duration with or without an increase in submental EMG in NREM sleep or with an increase in EMG tone in REM sleep.

For comparative purposes three definitions of arousals were used for scoring sleep records of control subjects. The first was the current American Sleep Disorders Association (ASDA) definition which defines an arousal as a return to EEG alpha or theta rhythm of at least 3 seconds duration with or without an increase in submental EMG in NREM sleep or with an associated increase in EMG for at least 3 seconds in REM sleep (Bonnet M et al, 1992). The second was the a modification of ASDA definition which defines an arousal as a return to EEG alpha or theta rhythm for at least 1.5 seconds irrespective of EMG in NREM sleep but accompanied by an increase in submental EMG for at least 1.5 seconds during REM sleep. The third definition of arousals was the one used in the pilot study whereby an arousal was defined as a return to alpha or theta EEG rhythm of at least 1.5

seconds with any increase in submental EMG irrespective of the ongoing sleep stage (Cheshire K et al, 1992).

As there is yet no standard definition of arousals, an attempt was made to visually identify in the EEG any atypical features, which might otherwise not be scored as 'arousals' as per current definitions, at the termination of apnoeas or hypopnoeas. An increase in EEG frequency of whatever duration or K complexes occuring near the end of obstructed respiratory events were specifically looked for. However, these EEG features were not found consistently through the various sleep stages within and between different subjects. Likewise, an attempt was also made to define an arousal as any return, howsoever brief, in the EEG to alpha or theta frequencies with an associated EMG criteria. This, however, led to difficulties in distinguishing true 'arousals' from sleep spindles which also exhibit EEG frequencies in the same range. For this reason, this definition of arousals was abandoned.

The exact number of 2%, 3% and 4% oxygen desaturations per hour were manually calculated for each subject from the overnight oxygen saturation tracing.

The rest of the polysomnographic measurements taken and their definitions are as for pilot study described in the previous chapter.

Reproducibility of scoring sleep studies

In 6 relatives and 6 control subjects, the sleep studies were analysed twice by the same investigator to examine the reproducibility of scoring. These 12 subjects covered a large range of observed abnormal breathing during sleep (median: 31, range: 6-88 A+H/hour of sleep) as from the initial sleep scoring results. Once selected, these sleep records were reanalysed by the polysomnographer after randomising them so that the results of the second scoring were unaffected by any memory of their initial scoring.

Two sets of polysomnographic data were thus obtained for each of the 12 subjects. These sleep parameters were total time spent awake in bed, total time spent in each of stages 1-4 of NREM sleep and in REM sleep, total number of apnoeas+hypopnoeas and arousals throughout the night and the number of 2%, 3% and 4% oxygen desaturations per hour.

The comparisions between two sets of data were performed by Pearson's correlation coefficient. Mean percentage difference (higher score-lower score/lower score x100) was also calculated for each sleep parameter in this group of 12 subjects (table 4.1). As correlation does not best indicate possible systematic differences, each sleep parameter was also shown as a plot of differences between the two measurements against their mean (Bland JM et al, 1986, Fig 4.1 to 4.3). These results suggest that

there is close agreement between the two scorings for all the polysomnographic parameters obtained and are well in keeping with previously published results on reproducibility of scoring respiratory events (Whyte KF et al, 1992).

Table 4.1 Reproducibility of sleep parameters

Sleep parameter	Correlation coefficient	Mean percentage difference (%)
Time awake	0.99	4
Stage 1 NREM	0.99	6
Stage 2 NREM	0.99	3
Stage 3 NREM	0.99	8
Stage 4 NREM	0.99	8
REM	0.99	4
A+H	0.99	5
Arousals	0.99	6
2%/hr desats	0.99	5
3%/hr desats	0.99	5
4%/hr desats	0.99	8

All correlation coefficients significant at $p<0.001$, A+H- total number of apnoeas plus hypopnoeas.

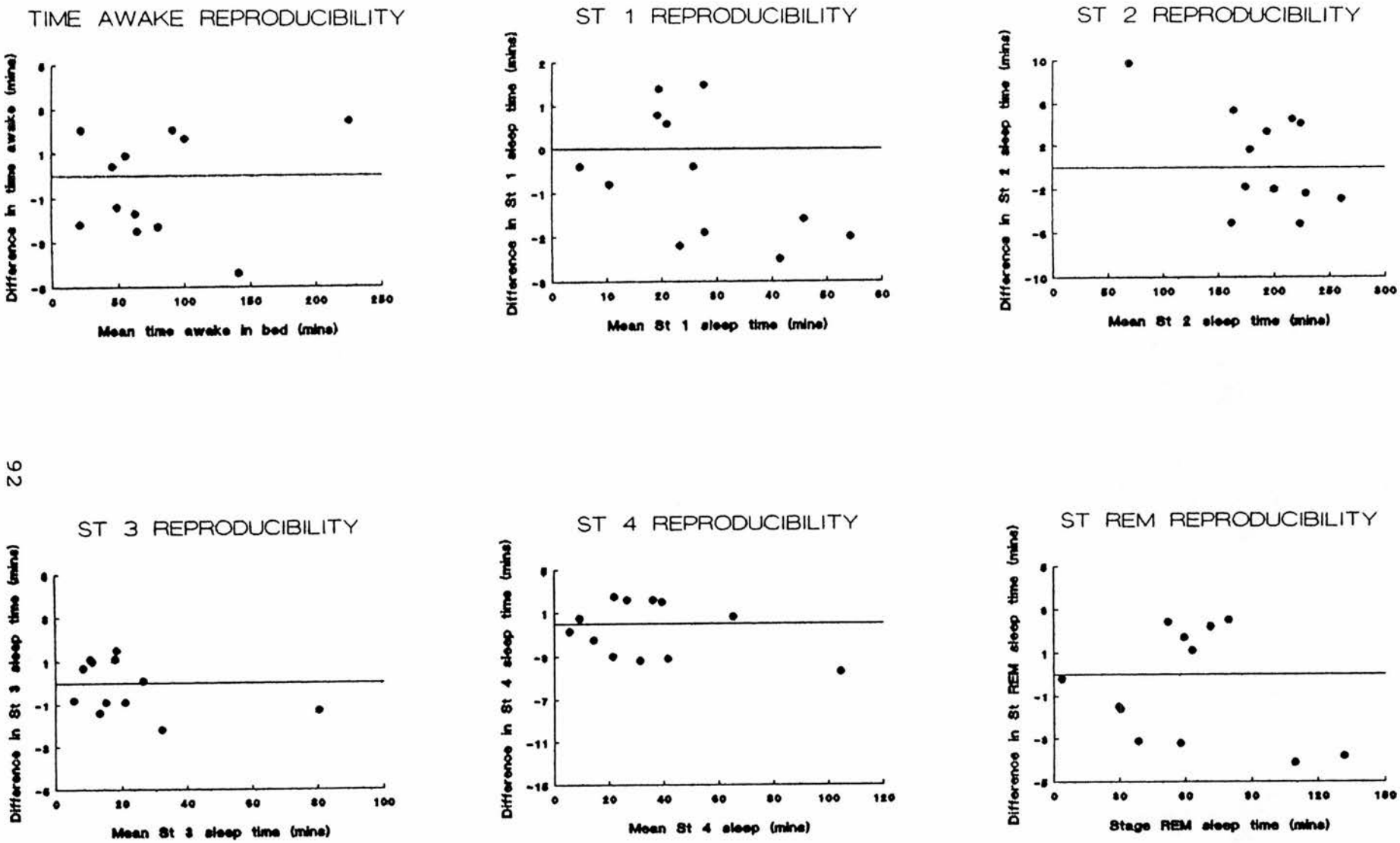

Fig 4.1 Bland and Altman graphs for sleep stage scoring reproducibility

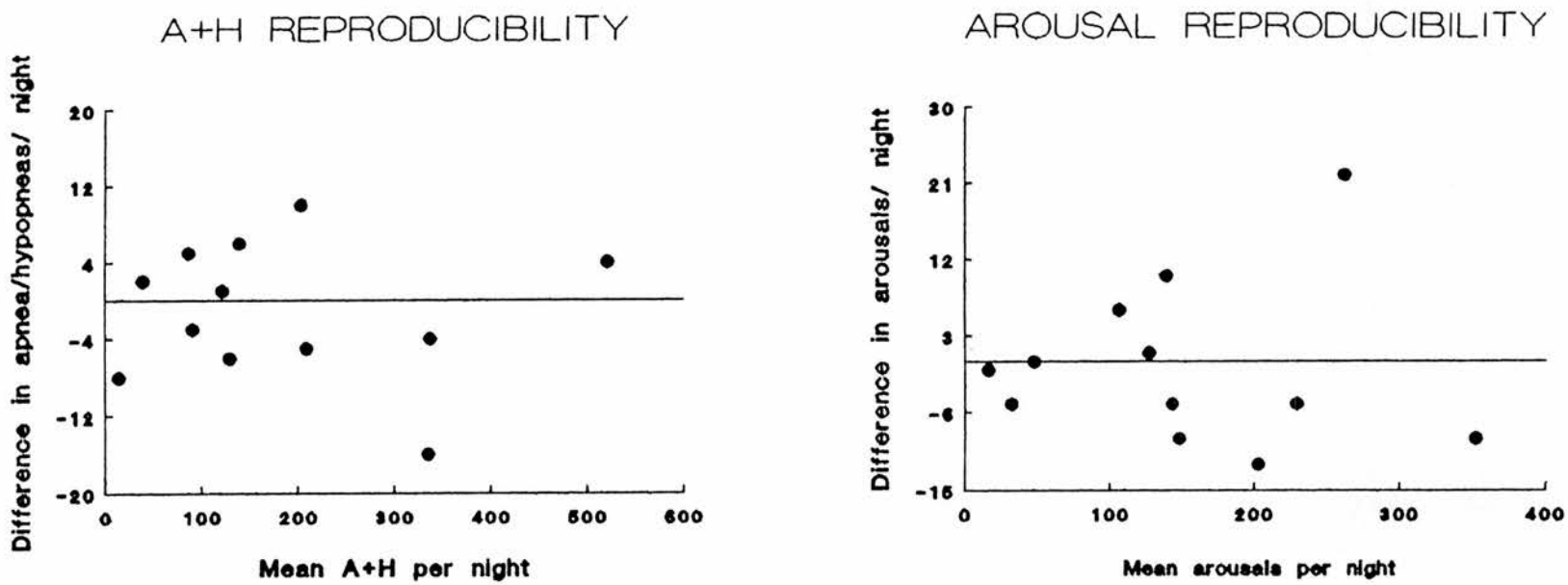

Fig 4.2 Bland and Altman graphs on apnoea+hypopnoea and arousal reproducibility

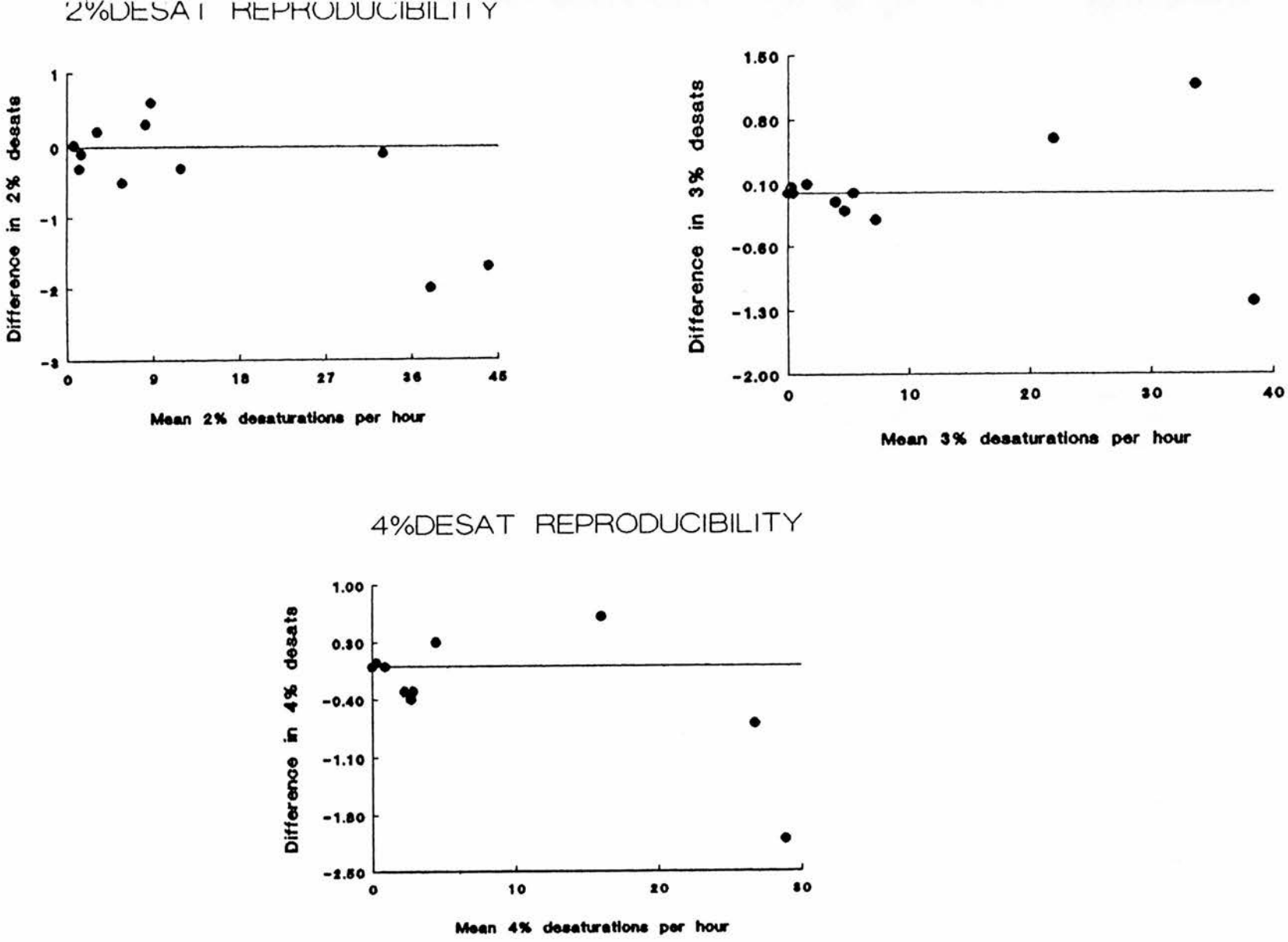

Fig 4.3 Bland and Altman graphs for desaturation reproducibility

The methodology and reproducibility of acoustic reflectance is given in chapter 6 while the methodology of cephalometry in chapter 3.

Statistical analyses

The various statistical tests as appropriate were performed using the SPSS/PC.

CHAPTER 5

RESULTS: CASE CONTROL FAMILY STUDY

RESULTS: CASE CONTROL FAMILY STUDY IN PATIENTS WITH SAHS

The results in this chapter are given in two separate sections, 5.1 and 5.2. Section 5.1 gives the recruitment, questionnaire and sleep study results in the relatives and control subjects while section 5.2 compares the results in the matched relative-control pairs. The first part of section 5.1 gives the results in all SAHS patients and all their relatives. The second part of section 5.1 gives the results in all control subjects.

Section 5.1- Results in the whole group

Results in index SAHS patients and their relatives

Patient recruitment

Over a 21 month period, from Nov 1991 to July 1993, 110 patients were diagnosed to be having SAHS on the basis of having more than 15 A+H/hour of sleep and at least 2 associated symptoms of SAHS. Out of these 110 patients 45 had a body mass index (BMI) of greater than 30 kg/m^2. Another 10 were excluded from the study because of having at least one of the conditions mentioned in the exclusion criteria in the previous chapter. A further 10 subjects, though otherwise eligible for participation, were still to be contacted in July 1993 when the study was terminated. Therefore 45 index SAHS patients (43 male) participated in the study. They had a mean (95% CI) age of 51 (28-71) years, BMI of 26.3 (22.6-29.9) kg/m^2, A+H of 42 (16-120) per hour of sleep and arousals (Cheshire K

et al, 1992) of 47 (13-139) per hour of sleep.

These 45 SAHS patients had a total of 130 first degree relatives. Twentyfive of the 130 relatives refused to participate in the study or were uncontactable. Therefore, no information is available on these 25. The remaining 105 relatives (51 male) participated in the study. They had a mean age of 40 (17-75) years.

Sleep questionnaire

Sleep questionnaire data was available in 103 of these 105 relatives. Two relatives did not return the questionnaire despite repeatedly being requested to do so. Questionnaire data was also available in 80 of the 82 relatives who underwent sleep studies. Only questionnaire but not sleep study data was available in 23 relatives.

Table 5.11 gives the summary of sleep symptom questionnaire data on 103 relatives. Seventy two of these 103 relatives had current bed partners who helped the relatives in answering the symptom questionnaire.

Table 5.11 Sleep symptom questionnaire data on 103 first degree relatives.

Collar size(cm)	mean 40.4	95% CI 35.7-43.2
Alcohol(u/wk)	mean 12.4	95% CI 0-35.3
Current smoking	39/103	
Alcohol at bedtime	13/103	
Significant past history	41/103	
Time to fall asleep	Immediately- 16/103 Within 20 mins- 49/103 Over 20 mins- 37/103	
Repeated awakenings	80/103	
Nocturnal choking	12/103	
Witnessed apnoeas	8/103 don't know- 28/103	
Restless sleep	27/103 don't know- 28/103	
Refreshing sleep	57/103	
Snoring	41/103 don't know- 9/103	
Excessive daytime sleepiness	54/103	
Sleeping against will	15/103	

Significant past history includes history of broken nose and nose or throat operations in the past.

Polysomnography

Sleep studies were done in 82 of the 105 relatives. Four of the 45 index patients had no living first degree relatives. All 6 eligible relatives of another 3 index patients refused sleep studies though 4 of them completed the questionnaire. Thus 38 (36 male) of the 45 index SAHS patients provided the 82 relatives who underwent sleep studies. The mean (95% CI) age of these 38 SAHS patients was 53 (28-71) years, BMI 26.6 (22.8-29.9) kg/m2, A+H 43 (16-120) per hour of sleep and arousals (Cheshire K et al, 1992) 47 (13-140) per hour of sleep. One hundred percent sleep study coverage was achieved in 20 families.

Table 5.12 gives the sleep study data on 82 (41 male) relatives. These 82 relatives had a mean (95% CI) age of 38 (17-73) years and BMI 25.3 (19.4-33.9) kg/m^2.

Table 5.12 Polysomnography data on 82 relatives

Parameter	Mean	95% CI
TIB(min)	427	363-468
Time awake(min)	62	5-204
Sleep Period Time(min)	404	308-454
Total Sleep Time(min)	342	125-429
Sleep Onset Latency(min)	23	3-79
Sleep Efficiency Index(%)	80	39-96
St 1 NREM(min)	20	3-52
St 2 NREM(min)	187	73-304
Light Sleep(min)	207	83-317
St 3 NREM(min)	17	4-50
St 4 NREM(min)	58	9-119
Slow Wave Sleep(min)	75	21-146
REM Sleep(min)	59	9-110
Movement Time(min)	1.8	0-30
Time awake% SPT	18	1-67
St 1 NREM% SPT	5	1-12
St 2 NREM% SPT	46	15-71
Light Sleep% SPT	51	18-74
St 3 NREM% SPT	4	1-12
St 4 NREM% SPT	14	2-30
Slow Wave Sleep% SPT	19	5-38
REM Sleep% SPT	14	3-27
Movement Time% SPT	0.4	0-7
REM Sleep Latency(min)	130	41-299
A+H/hour of sleep	15	2-68
Arousals/hr slept (Cheshire K et al, 1992)	15	5-42
3SecA (/hour of sleep)	35	20-79
1.5SecA (/hour of sleep)	35	21-85
2% oxygen desaturation/hr	5	0-33
3% oxygen desaturation/hr	3	0-22
4% oxygen desaturation/hr	2	0-17

3SecA- Number of arousals per hour of sleep and defined as return to alpha or theta EEG rhythm for at least 3 seconds irrespective of EMG in NREM sleep but accompanied by an increase in submental EMG tone in REM sleep.

1.5SecA- Number of arousals per hour of sleep and defined as return to alpha or theta EEG rhythm for at least 1.5 seconds irrespective of EMG in NREM sleep but accompanied by an increase in submental EMG tone in REM sleep.

Arousal definition by Cheshire K et al, 1992- A return to alpha or theta EEG rhythm for at least 1.5 seconds accompanied by any rise in submental EMG tone.

Of the 82 relatives who underwent sleep studies 71 had more than 5 A+H/hr of sleep, 51 had more than 10 A+H/hr of sleep and 33 had more than 15 A+H/hr of sleep. Six out of 82 relatives sleep studied had more than five 4% oxygen desaturations per hour.

Effect of sex, age and BMI on A+H/hour of sleep in relatives

There was no effect of sex on A+H/hr slept between 42 male and 40 female unmatched relatives (A+H males 16 SEM 2/hr slept vs females 14 SEM 2/hr; p=0.6). Multiple linear regression was performed to find the effect of age and BMI on A+H per hour of sleep in 82 relatives. Both age (p=0.003, r=0.4) and BMI (p=0.003, r=0.4) correlated with A+H/hr (fig 5.11) and accounted for 26% of the variability in this parameter.

Effect of age, sex and BMI on arousals in relatives.

The effect of sex was tested between sexes on arousals defined by all three definitions used in table 5.12. Comparision between sexes was done by unpaired t test. No difference between sexes was found in the number of arousals/hr irrespective of the arousal definition tested (table 5.13).

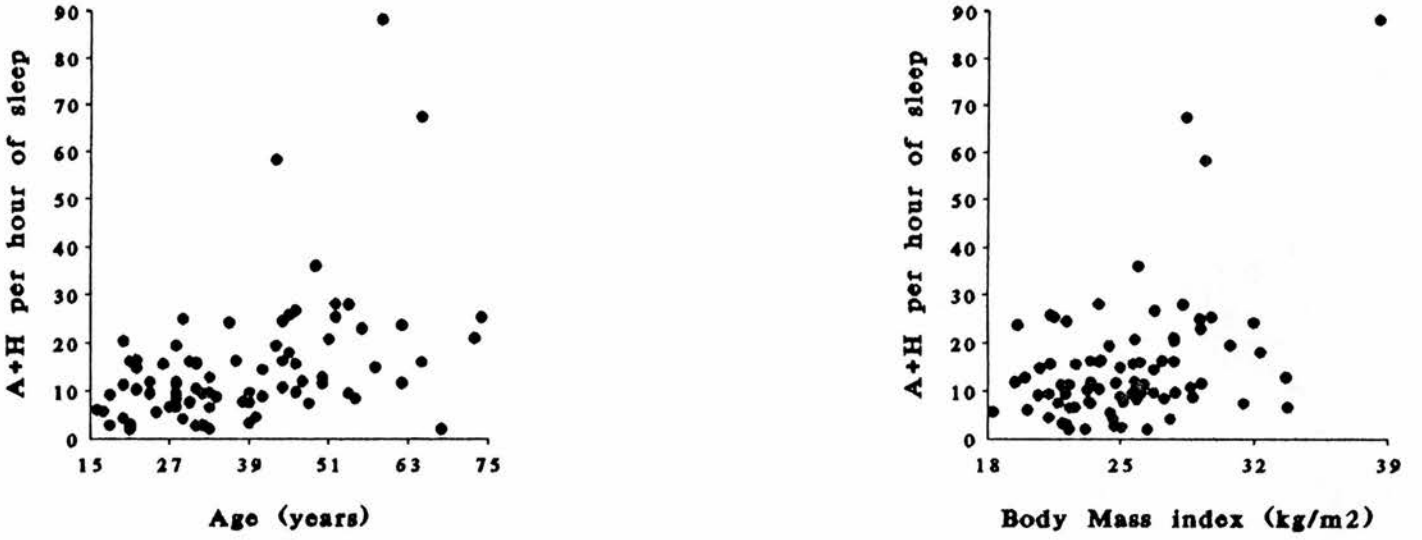

Fig 5.11 Effect of age and body mass index on A+H per hour of sleep

Table 5.13 Effect of sex on arousals in relatives

Definition	Men	Women	P
Arousals/hr (Cheshire K et al, 1992)	17 SEM 2	13 SEM 1	0.1
3SecA	37 SEM 2	32 SEM 2	0.1
1.5SecA	37 SEM 2	33 SEM 2	0.1

3SecA and 1.5SecA as defined in table 5.12

Multiple linear regression was performed to find the effect of age and BMI on arousals in all relatives. Age correlated strongly with arousals (p=0.0001), defined by all three definitions, explaining 13-28% of the observed variability. There was no correlation between BMI and arousals (p=0.8, 0.2 and 0.1 for above three arousal definitions respectively).

Combining questionnaire and polysomnography results

Eighty of the 82 patients who underwent polysomnography completed the questionaire. Excessive daytime sleepiness was considered present if the subjects averaged two naps per day when not in bed.

Out of 33 relatives with more than 15 A+H/hr of sleep, 19 had excessive daytime sleepiness, 12 of these being snorers. Seven snored but were not sleepy.

Out of 51 relatives with more than 10 A+H/hr of sleep, 30 had excessive daytime sleepiness, 17 of these being snorers. Ten snored but were not sleepy.

Results in the control group

Recruitment

55 of 59 controls approached agreed to participate in the study. All 55 (30 male) completed symptom questionnaire and underwent sleep studies. These 55 controls had a mean (95% CI) age of 37 (18-71) years and BMI 24.4 (19.1-34.1) kg/m^2. Forty seven of them were under 60 years of

age.

Sleep Questionnaires

Table 5.14 gives the questionnaire results in 55 control subjects. Forty of them had current bedpartners who helped them with some of the questions in the questionnaire.

Table 5.14 Questionnaire results in 55 control subjects

Collar size(cm)	Mean 40.4	95% CI 36.8-43.2
Alcohol(u/wk)	Mean 9.6	95% CI 0-30
Current smoking	10/55	
Bedtime alcohol	13/55	
Significant past history	14/55	
Sleep to fall asleep	Immediately- 6/55 Within 20 mins- 40/55 More than 20 mins- 9/55	
Repeated awakenings	37/55	
Nocturnal choking	1/55	
Nocturia	38/55	
Eneuresis	1/55	
Witnessed apnoeas	2/55 don't know- 11/55	
Restless sleep	14/55 don't know- 16/55	
Morning headache	1/55	
Refreshing sleep	34/55	
Loud snoring	10/55 don't know- 3/55	
Excessive daytime sleepiness	16/55	
Sleeping against will	2/55	
Diminished libido	8/55 not reported- 14/55	
Irritability	4/55 not reported- 5/55	
Weight gain	16/55	
Pedal oedema	1/55	

Polysomnography

Sleep study data in 55 control subjects (normative data) is given in table 5.15.

Table 5.15

Parameter	Mean	95% CI	90% CI
Time in Bed(min)	421	287-482	369-456
Sleep Period Time(min)	399	274-466	340-437
Total Sleep Time(min)	334	98-430	106-412
Sleep Onset Latency(min)	23	2-92	4-71
Sleep Efficiency Index(%)	79	23-96	40-94
Time awake(min)	63	8-284	9-221
St 1 NREM(min)	19	4-56	5-43
St 2 NREM(min)	162	46-260	56-236
Light Sleep(min)	181	60-280	74-269
St 3 NREM(min)	18	1-64	3-35
St 4 NREM(min)	72	2-150	17-134
Slow Wave Sleep(min)	90	5-181	24-157
REM Sleep(min)	62	1-123	10-112
Movement Time(min)	1	0-25	0-9
Time awake %SPT	16	2-74	2-57
St 1 NREM% SPT	5	1-13	1-10
St 2 NREM% SPT	40	14-64	17-59
Light Sleep% SPT	45	19-69	21-65
St 3 NREM% SPT	5	0-16	1-9
St 4 NREM% SPT	18	1-36	4-33
Slow Wave Sleep% SPT	22	1-43	7-39
REM Sleep% SPT	15	1-29	3-27
Movement Time% SPT	0	0-7	0-2
REM Sleep Latency(min)	123	44-337	53-300
A+H/hr of sleep	7	0-52	0-19
Arousals/hr slept (Cheshire K et al, 1992)	14	3-55	5-34
Arousals/hr slept (Bonnet M et al, 1992)	21	7-56	8-46
Arousals/hr slept (Rev 1.5 sec def.)	26	5-67	10-55
2% oxygen desats/hr	3	0-31	0-11
3% oxygen desats/hr	2	0-28	0-7
4% oxygen desats/hr	1	0-17	0-5

SPT- Sleep Period Time

Arousals (Bonnet M et al, 1992) defined as per current ASDA guidelines of a return to alpha or theta EEG rhythm for at least 3 seconds irrespective of EMG activity in NREM sleep but accompanied by a rise of at least 3 seconds submental EMG tone in REM sleep.

Rev 1.5 sec def.- In house definition of arousals defined as a return to alpha or theta EEG rhythm for at least 1.5 seconds irrespective of EMG activity in NREM sleep but accompanied by a rise of at least 1.5 seconds submental EMG tone in REM sleep.

Arousals (Cheshire K et al, 1992) defined as in table 5.12

Sleep study data on 47 controls under 60 years of age is given in table 5.16. These 47 controls had a mean (95% CI) of 32 (18-58) years and BMI 24 (18.8-32.5) kg/m^2.

Table 5.16

Parameter	Mean	95% CI	90% CI
Time in Bed(min)	427	379-490	387-457
Sleep Period Time(min)	405	343-469	359-446
Total Sleep Time(min)	351	126-432	221-416
Sleep Onset Latency(min)	22	2-96	4-68
Sleep Efficiency Index(%)	82	29-96	55-95
Time awake(min)	54	8-232	9-155
St 1 NREM(min)	18	4-57	5-44
St 2 NREM(min)	168	61-262	76-246
Light Sleep(min)	186	74-280	90-270
St 3 NREM(min)	20	2-72	4-37
St 4 NREM(min)	78	21-153	26-138
Slow Wave Sleep(min)	98	34-186	46-162
REM Sleep(min)	67	4-126	16-113
Movement Time(min)	1	0-20	0-0
Time awake %SPT	14	2-65	2-41
St 1 NREM% SPT	4	1-14	1-11
St 2 NREM% SPT	41	18-64	20-61
Light Sleep% SPT	46	21-70	24-65
St 3 NREM% SPT	5	0-18	1-9
St 4 NREM% SPT	19	5-36	6-33
Slow Wave Sleep% SPT	24	9-44	11-40
REM Sleep% SPT	17	1-29	4-28
Movement Time% SPT	0	0-5	0-0
REM Sleep Latency(min)	125	41-346	53-305
A+H/hr of sleep	6	0-30	0-14
Arousals/hr slept (Cheshire K et al, 1992)	12	3-37	5-27
Arousals/hr slept (Bonnet M et al, 1992)	18	7-47	8-41
Arousals/hr slept (Rev 1.5 sec def.)	23	4-53	8-40
2% oxygen desats/hr	3	0-30	0-10
3% oxygen desats/hr	2	0-26	0-7
4% oxygen desats/hr	1	0-16	0-5

Definition of arousals as in table 5.14

Three of the 55 control subjects had more than five 4% oxygen desaturations/hour. Of the 55 controls 3 (all men) had more than 15, 9 (7 men) had more than 10 and 28 (17 men) had more than 5 A+H/hour of sleep.

Combining questionnaire and polysomnography results

Out of 3 controls with >15 A+H/hr of sleep 1 had excessive daytime sleepiness, none reported loud snoring and none reported both these symptoms. Out of 9 controls with >10 A+H/hr of sleep, 4 had excessive daytime sleepiness, 1 of them being a snorer. One snored but was not sleepy.

Effect of age, sex and BMI on A+H/hr in control subjects

There was no effect of sex between 30 men and 25 women on A+H/hour of sleep (median A+H in men 4.4/hr of sleep vs median A+H in women 3.6/hr of sleep, $p=0.4$) though 7 of the 9 controls with >10 A+H per hour of sleep and all 3 with >15 A+H/hr were men. Multiple linear regression was performed to find the effect of age and BMI on A+H per hour of sleep in 55 control subjects. Age correlated strongly with A+H/hr ($p=0.0007$, $r=0.5$), explaining 25% of the observed variability. There was no correlation between BMI and A+H/hr ($p=0.4$, $r=0.2$).

Effect of age, sex and BMI on arousals in control subjects

The effect of sex was tested between 30 men and 25 women on arousals defined by all three definitions. There was

no significant difference between these sexes for age (men 40 SEM 3, women 33 SEM 2, p=0.1). Comparision between sexes was done by unpaired t test. No difference between sexes was found in the number of arousals/hr irrespective of the arousal definition tested (table 5.17).

Table 5.17 Effect of sex on arousals in control subjects

Definition	Men	Women	P
Arousals/hr (Cheshire K et al, 1992)	16 SEM 2	12 SEM 2	0.1
3SecA	22 SEM 2	21 SEM 2	0.8
1.5SecA	26 SEM 3	24 SEM 2	0.5

3SecA and 1.5SecA as defined in table 5.12

Multiple linear regression was performed to find the effect of age and BMI on arousals in 55 control subjects. Age correlated strongly with arousals ($p<0.001$), defined by all three definitions, explaining 26-36% of the observed variability. There was no correlation between BMI and arousals ($p=0.4$).

Section 5.2- Results in matched pairs

Recruitment

Thirty eight index SAHS patients provided 82 relatives who underwent sleep studies. The first 51 of these 82 relatives were matched one for one with controls. Six of the 38 index SAHS patients were recruited towards the latter half of the study and none of their relatives were included in the match. Therefore 32 index patients provided at least one relative included in the matching.

These 32 index patients (31 male) had a mean (95% CI) age of 51 (28-68) years, BMI of 26.5 (22.8-29.9) kg/m^2, A+H of 39 (16-105) / hour of sleep, arousals of 44 (13-140) /hour of sleep and a collar size of 40 (38-43) cm.

These 32 index patients had a total of 108 first degree relatives. Ninety one of 108 relatives agreed to participate in the study and 17 refused or were uncontactable. Of the 91 relatives who participated only questionnaire data was available in 16. All of the remaining 75 relatives underwent sleep studies and 74 of these completed the questionnaire.

There were no differences between 51 matched and 40 unmatched relatives in any of the sleep related symptoms (table 5.21). However, the 51 matched relatives were younger (age 36 SEM 2 vs 44 SEM 3 years, p=0.02) and consumed less alcohol (8 SEM 1 vs 12 SEM 2 u/wk, p=0.04) than the 40 unmatched relatives and proportionately fewer were current smokers (14/50 vs 19/40, p=0.02).

Table 5.21 Comparision of sleep related symptoms between 51 matched with 40 unmatched relatives.

Symptom	Matched relatives	Unmatched relatives	P
Snoring	24/50	14/33	0.6
Excessive daytime sleepiness	28/50	20/40	0.6
Sleeping against will	9/50	3/40	0.3
Witnessed apnoeas	4/50	3/40	0.9
Nocturnal choking	8/50	3/40	0.4
Refreshing sleep	26/50	24/40	0.5

Out of 55 controls recruited 4 were found to have a different age, height or weight than what was recorded in their general practitioner's case notes. Therefore 51 controls were matched to 51 relatives on a one to one basis (table 5.22).

Table 5.22 Matching characteristics of the two groups

	Relatives	Controls
n	51	51
Male	25	25
Age(years)	36 SD 14	35 SD 14
BMI(kg/m^2)	24 SD 4	24 SD 3

Questionnaire data

Questionnaire data was available in 50 matched pairs. There was no difference between groups in smoking habits, alcohol consumption or collar size. More relatives than controls reported loud snoring, excessive daytime sleepiness and nocturnal choking (table 5.23).

Table 5.23 Sleep symptoms that were significantly different between relatives and matched controls in 50 pairs.

Symptom	Relatives	Controls	P
Loud snoring	24	6	0.0002
Nocturnal choking	8	1	0.01
Excessive daytime sleepiness	28	16	0.01
Sleeping against will	10	2	0.01

Table 5.24 gives sleep symptoms whose frequency was not different between relatives and controls in 50 matched pairs.

Table 5.24 Non significant differences in questionnaire data between relatives and controls in 50 matched pairs.

Parameter	Relatives	Controls	P
Collar size(cm)	40 SEM 0.4	40 SEM 0.3	0.4
Alcohol(u/wk)	8 SEM 1	8 SEM 1	0.9
Current smokers	14	8	0.3
Witnessed apnoeas	4	2	0.5
Refreshing sleep	26	30	0.4
Restless sleep	13	12	0.9
Repeated awakenings	35	32	0.5
Morning headache	7	1	0.06
Nocturia	39	34	0.3
Irritability	6	4	0.4
Enuresis	2	1	0.6
Decreased libido	8	8	1.0
Weight gain	19	16	0.5
Pedal oedema	3	1	0.6

Sleep studies

When compared to controls (fig 5.21) the relatives had higher A+H/hr (relatives median 13, controls median 4 A+H/hr, $p<0.0001$). The relatives also had more arousals (3SecA) than controls (relatives median 30/hr, controls median 17/hr, $0<0.0001$, fig 5.22). The relatives had a greater sleep disturbance with more light sleep and less slow wave sleep than controls (table 5.25). There were no significant differences between relatives and controls in other sleep parameters (table 5.26) in these 51 matched pairs.

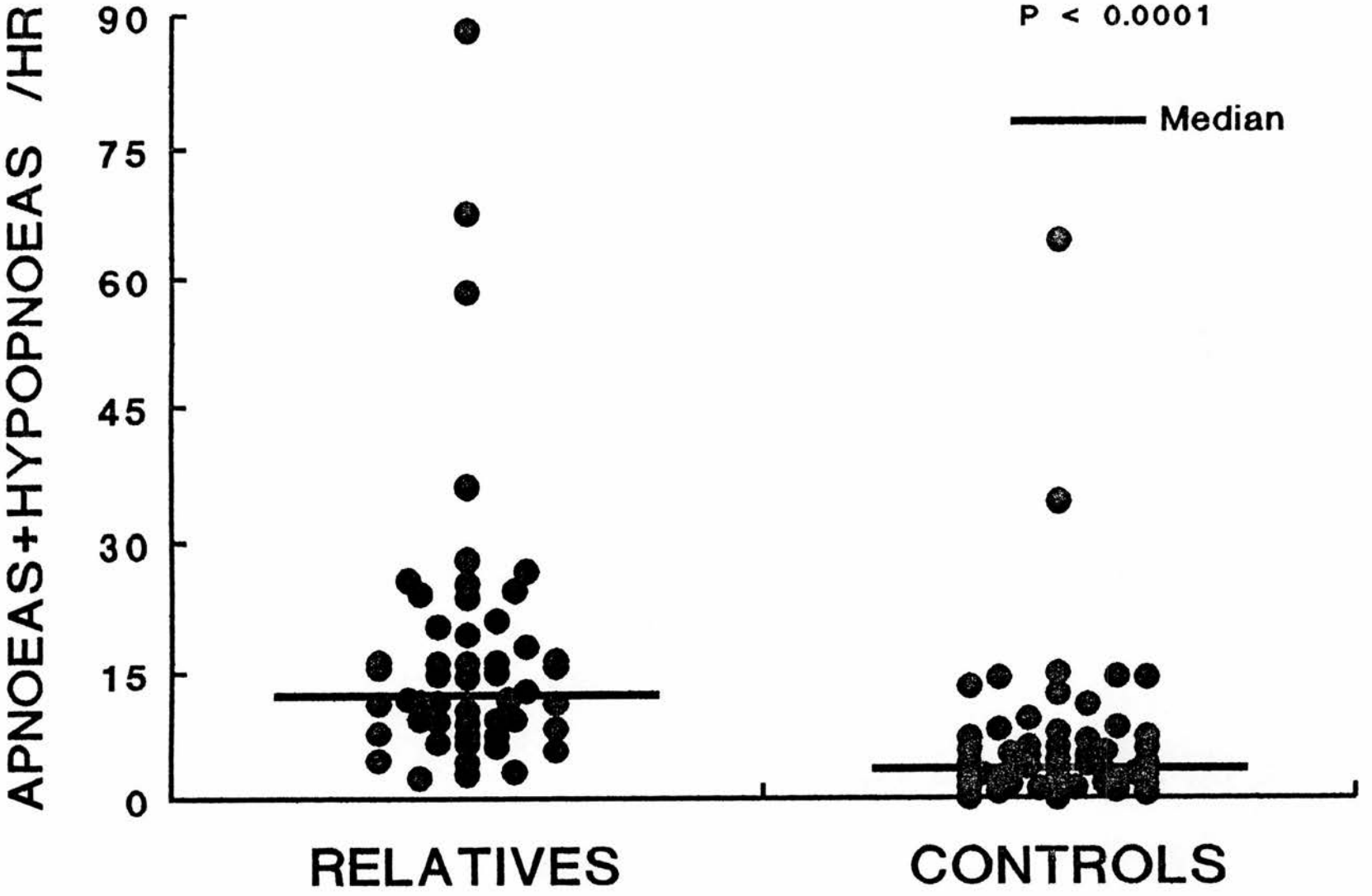

Fig 5.21 Relatives had higher A+H/hr than controls

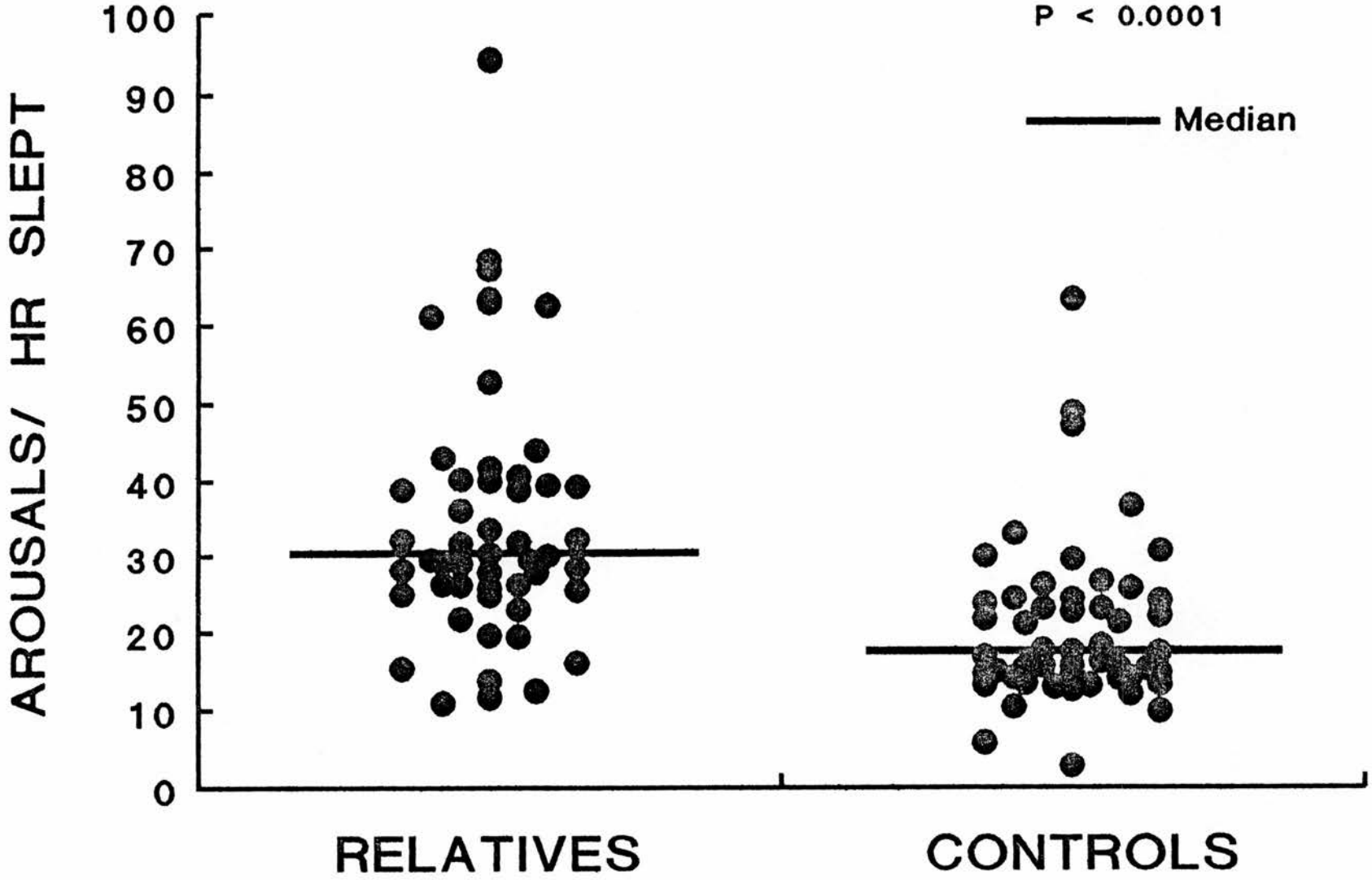

Fig 5.22 Relatives had higher arousals/hr than controls

Table 5.25 Relatives had a different sleep architecture than controls

Sleep stage	Relatives	Controls	P
St 2 NREM(min)	188 SEM 6	160 SEM 7	0.005
St 4 NREM(min)	61 SEM 4	73 SEM 5	0.03
Light Sleep(min)	209 SEM 7	179 SEM 8	0.006
Slow Wave Sleep(min)	78 SEM 5	91 SEM 5	0.03
St 2 NREM% SPT	46 SEM 1	40 SEM 2	0.02
St 4 NREM% SPT	15 SEM 1	18 SEM 1	0.01
Light Sleep% SPT	51 SEM 2	45 SEM 2	0.02
Slow Wave Sleep% SPT	19 SEM 1	23 SEM 1	0.01

SPT- Sleep Period Time

Table 5.26 Sleep parameters which did not differ between relatives and controls in 51 matched pairs

Sleep parameter	Relatives	Controls	P
Time in bed(min)	427 SEM 3	423 SEM 5	0.4
Sleep Period Time(min)	408 SEM 4	400 SEM 5	0.3
Total Sleep Time(min)	349 SEM 9	333 SEM 11	0.3
Sleep Onset Latency(min)	20 SEM 2	22 SEM 3	0.4
Sleep Efficiency Index(%)	81 SEM 2	79 SEM 2	0.3
Time awake(min)	58 SEM 7	65 SEM 9	0.5
ST 1 NREM(min)	21 SEM 2	19 SEM 2	0.4
St 3 NREM(min)	17 SEM 1	18 SEM 2	0.6
REM sleep(min)	61 SEM 4	62 SEM 4	0.8
Time awake% SPT	18 SEM 4	17 SEM 2	0.8
St 1 NREM% SPT	5 SEM 0.4	5 SEM 0.4	0.5
ST 3 NREM% SPT	4 SEM 0.3	5 SEM 0.4	0.4
REM sleep% SPT	15 SEM 1	15 SEM 1	0.7
REM Latency(min)	136 SEM 9	124 SEM 10	0.4

SPT- Sleep Period Time

In the 51 matched pairs, more relatives than controls had greater than 5, 10 and 15 A+H/hour sleep (table 5.27)

Table 5.27 Number of relatives and matched controls having A+H/hr over different thresholds.

Threshold A+H/hr	Relatives	Controls	P
5	47	24	<0.0001
10	33	9	<0.0001
15	23	3	<0.0001

The relatives had more 2% and 3% oxygen desaturations than controls but there was no difference in the frequency of 4% oxygen desaturations between relatives and controls (table 5.28).

Table 5.28 Comparision of oxygen desaturation data between relatives and controls.

Desaturations	Relatives	Controls	P
2%/hr	6 SEM 1	3 SEM 1	0.04
3%/hr	4 SEM 1	2 SEM 1	0.04
4%/hr	2 SEM 1	1 SEM 0.4	0.1

CHAPTER 6

UPPER AIRWAY MEASUREMENTS

Acoustic reflectance

Acoustic reflectometry is a technique that can provide non invasive estimates of airway cross sectional areas in reference to distance from the incisors. This is done by sending an acoustic pulse down a wavetube and into a subject's airway. The resultant reflections are recorded by a pressure sensitive microphone and computer system. Signal analysis consists of separation of the reflected wave, deconvolution by the incident pulse shape and airway cross sectional area construction. This area is displayed as a function of distance (Marshall I et al, 1993).

This reflectometer is portable, simple to use and provides a 'real time' display of airway area. The system is based on a standard microcomputer and permits the subject to breathe freely room air between measurements. Helium-oxygen gas mixture, as originally used by Fredberg JJ et al, 1980, is not required.

The reflectometer setup is shown in fig 6.1. A loudspeaker is acoustically coupled to one end of a wave tube and a pressure sensitive microphone is mounted in the tube wall near the distal end. The subject is connected to this end via a mouthpiece. The loudspeaker to microphone distance is 113 cm and the microphone to mouthpiece distance is 13 cm. The internal diameter of

the tube is 16 mm. The dead space in the system is approximately 10 ml.

Subjects breathe via a hole in the tube wall immediately proximal to the mouthpiece. To avoid spurious reflections, the hole is closed by a sliding respiratory shutter valve 100 ms before an airway measurement is made. This valve reopens 50 ms afterwards.

A sliding calibration valve just distal to the microphone permits the wave tube to be closed during calibration of the apparatus. Airway pressure is monitored by a pressure transducer connected to the mouthpiece to detect respiration and allow synchronization of airway measurements with the phase of breathing.

The loudspeaker is driven to produce a short duration Gaussian pressure pulse with a nominal full width at half maximum (FWHM) of 100 ms. This allows temporal separation of the incident from the reflected waveform even with a very short microphone to mouthpiece distance.

Though the loudspeaker's natural impulse response lasts about 2 ms, application to the loudspeaker of a calculated drive waveform (calculated as part of calibration procedure by frequency domain inverse filter method) results in a final incident Gaussian pressure pulse with a FWHM of 100 ms. The peak pulse pressure of the incident wave is approximately 200 Pa. The microphone (Type BL 1785, Knowles Electronics) has a

sensitivity of 3 mv/Pa and therefore produces a signal of 600 mv in response to the Gaussian pressure pulse. The reflections of interest are typically 30 dB below this level, ie 20 mv. In the measurement bandwidth (60 Hz-12 KHZ) the electronic noise from the microphone is 300 microvolts peak to peak, so that the subject to noise ratio is 30-40 dB. This has been previously found adequate for the reconstruction algorithm (Ware JA et al, 1969).

A microcomputer (10 MHZ, 80286, IBM compatible) drives the loudspeaker and collects the signal from the microphone preamplifier via a custom high speed analogue interface card. This card uses buffer memory techniques to achieve simultaneous analogue output and input at a 40 KHz sampling rate. The loudspeaker drive waveform is downloaded from the computer into buffer memory and then automatic high speed output to a Digital to Analogue Converter (DAC) and power amplifier is initiated. Likewise, the microphone signal is sampled at high speed by an Analogue to Digital Converter (ADC), while the data being stored in a second buffer memory. The data is then uploaded to the computer.

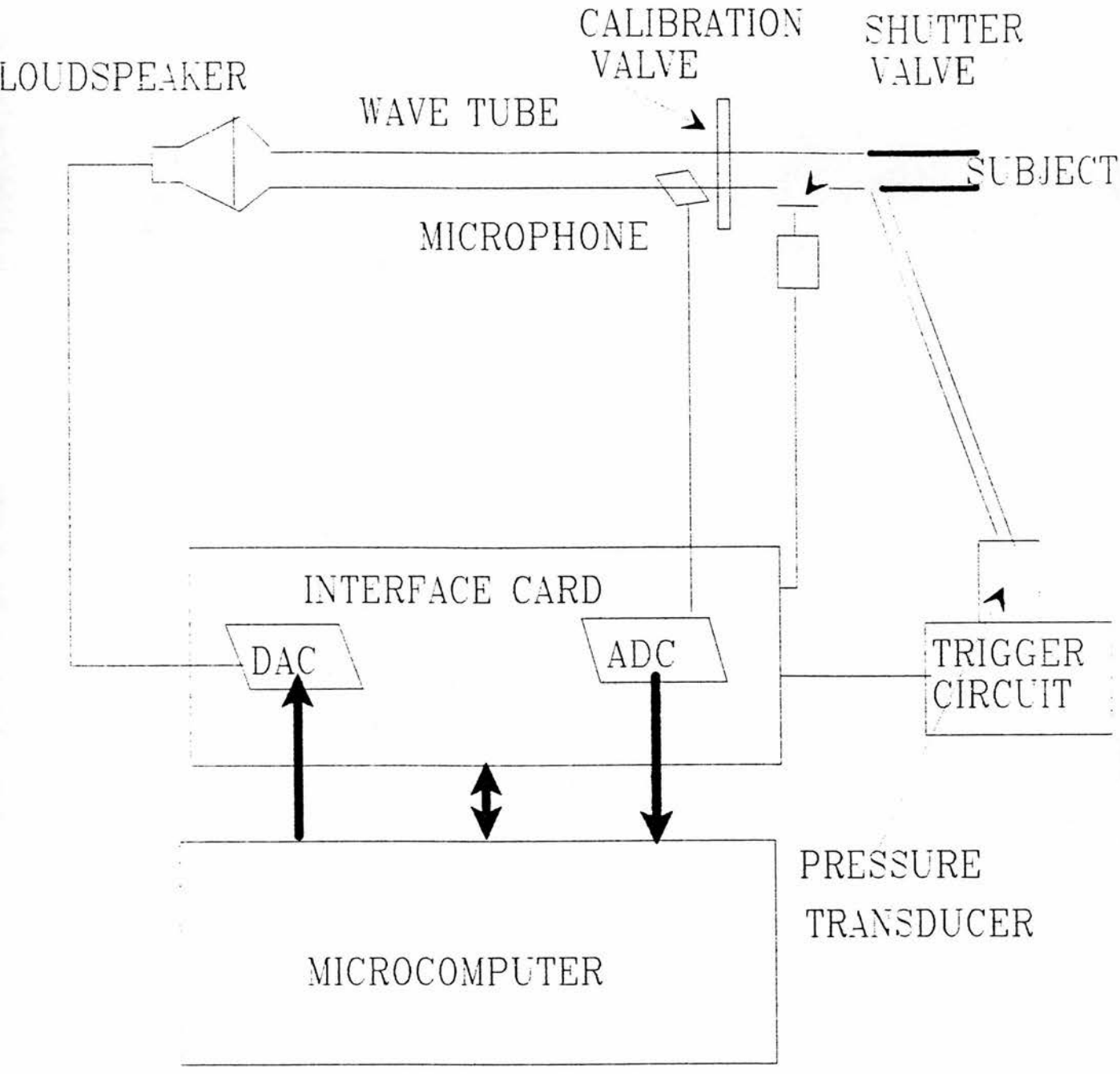

FIG 6.1 ACOUSTIC REFLECTOMETER

Reflectometer operation

1. Calibration of the instrument was done by closing the sliding valve to occlude the wave tube immediately beyond the microphone. The impulse response of the loudspeaker/wave tube/ microphone combination was measured and the drive waveform necessary to produce a Gausssian pulse calculated. This was then applied to the loudspeaker and the actual pressure pulse achieved was recorded.

2. The slide valve was opened and the subject coupled to the equipment by a mouthpiece. The subject sat upright with the head in neutral position and was asked to breathe normally through the mouthpiece. Though nose clips were not applied, care was taken to ensure that the subject did nor breathe through the nose during the measurements.

3. Measurements were taken at functional residual capacity (FRC) as the computer repeatedly closed the respiratory shutter valve, excited the loudspeaker, recorded the pressure wave and reopened the valve. Separation, deconvolution and area reconstruction followed each excitation using the reconstruction algorithm (Ware JA et al, 1969). An average of 5 measurements gave the final area distribution curve.

Though the pressure transducer coupled to the mouthpiece allows mointoring of airway pressure and synchronization

of the measurement to the phase of respiration, measurements can also be taken at various times in the respiratory cycle in an unsynchronized mode.

A typical area distance curve obtained at FRC with the subject breathing through the mouth is shown in fig 6.2. The positions of the anatomical landmarks on this acoustic curve were obtained from upper airway midline saggital MRI images as described elsewhere (Marshall I et al, 1993). They have also been confirmed by different breathing manoeuvers including glottic closure and directly measuring the distance from the incisors by fibreoscopy.

The upper airway distances are measured from the incisors (I). The first large deflection after the incisors is the mouth (M) and the first point showing the smallest area immediately after the mouth is the oropharyngeal junction (OPJ). This generally falls 100-150 mm from the incisors.

The part of the curve after oropharyngeal junction is the pharynx. The point on the acoustic curve showing the smallest area immediately after the pharynx and generally 170-220 mm from the incisors is the glottis (GLO). The location of the glottis can also be verified by noting the variability in the area measurements at this point on the curve, depending upon the positions of the vocal cords. The remaining curve after the glottis represents reflections from the trachea.

Thus, the part of the curve between oropharyngeal junction and glottis is the pharynx. The parameters which were measured from this curve were oropharyngeal junction area, glottic area, maximum pharyngeal area (MPA-defined as the largest area anywhere on the curve between OPJ and GLO), average pharyngeal area (APA) and pharyngeal volume (PV) obtained by integrating the area from OPJ to GLO over distance.

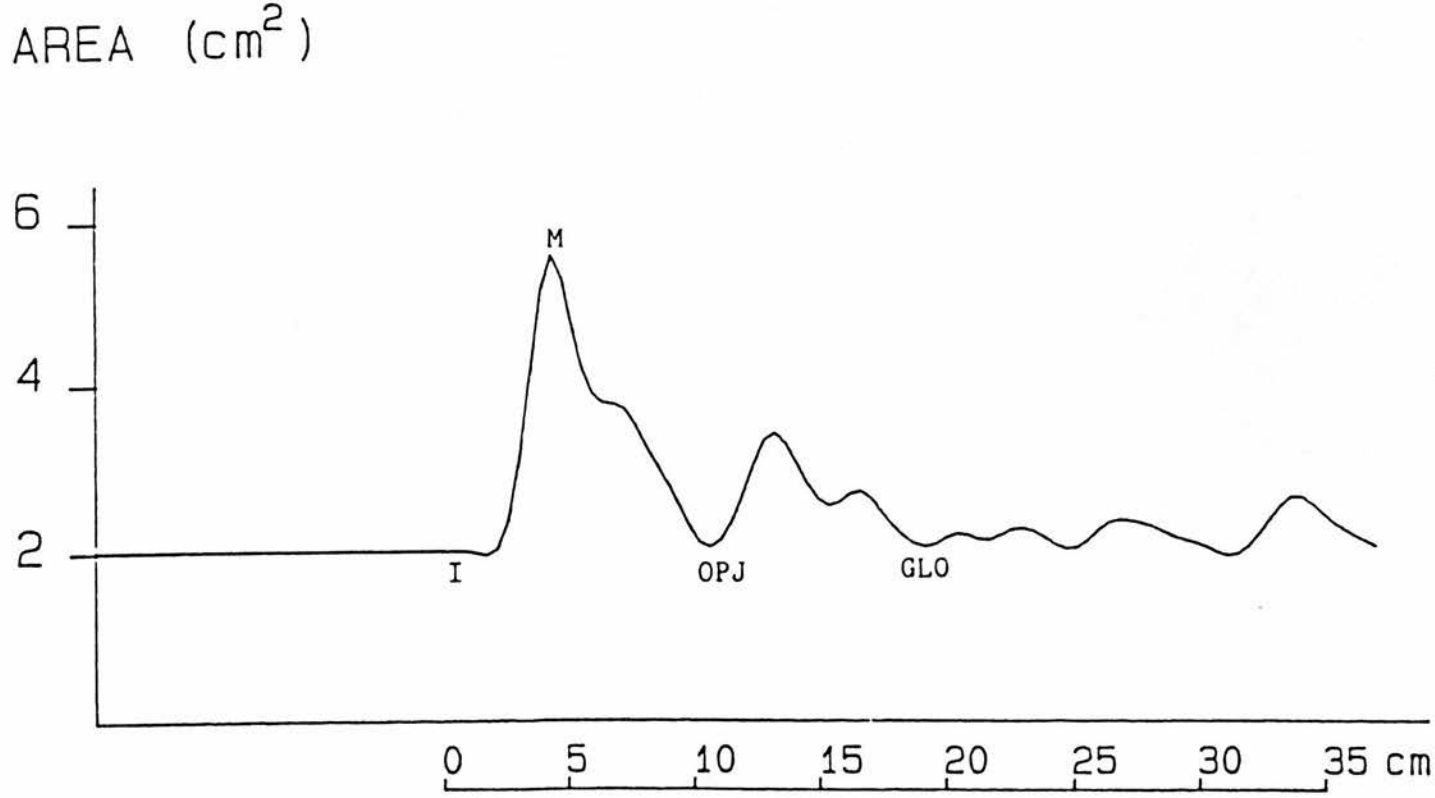

Fig. 6.2 Upper airway area - distance curve. I - incisors, M - mouth, OPJ - oropharyngeal junction, GLO - glottis. The curve between OPJ and GLO is the pharynx.

Reproducibility of acoustic reflectance measurements

Day to day within subject variability of acoustic reflectance measurements was tested in 6 female subjects recruited from the laboratory staff. None of these had any respiratory or sleep related problems. They had a mean (SD) age of 30 (6) years and mean (SD) BMI of 21.4 (3) kg/m^2. The equipment and the protocol was explained to them.

In all 6 subjects, acoustic measurements of the upper airway were taken on 8 successive days. On each day the measurements were taken between 10 am and noon with the subjects sitting and breathing normally through the mouth keeping the head in the neutral position. All the measurements were taken at FRC.

For each subject the mean and SD of 8 measurements for each acoustic parameter was calculated. SD/mean x 100 for each parameter in that subject gave the within subject coefficient of variation (CV) for that parameter (table 6.1). The average of all CVs for a given parameter in all 6 subjects gave the overall CV for that acoustic parameter.

The overall CV for oropharyngeal junctional cross sectional area (OPJ) was 12 SD 6%, maximam pharyngeal cross sectional area (MPA) 11 SD 3%, glottic cross sectional area (GLO) 15 SD 6%, average pharyngeal cross sectional area (APA) 7 SD 2% and pharyngeal volume (PV)

10 SD 3%. Larger variabilities were seen in OPJ and GLO cross sectional areas as these parts may be the most variable parts of the upper airways. APA and PV during wakefulness were found to be the most reproducible measurements. Measuring APA minimises the error caused by longitudinal shift and eliminates the necessity of comparing pharyngeal areas at a single distance from the mouth, which may correspond to different anatomic locations depending upon posture (Brown IB et al, 1987).

The mean day to day CV for the whole upper airway in all subjects was 11%. This is acceptable in a clinical physiological technique.

These results are consistent with the 20% day to day CV for acoustic measurements reported by Marshall I et al, 1993. They found the day to day CV in 5 subjects over 21 days as 13±3% for oropharyngeal area and 11±3% for maximum pharyngeal and glottic areas. Likewise, Brookes LJ et al, 1984, reported a 9±4% day to day CV for acoustic measurements using his more complex and clumsy equipment.

The effect of day to day variability on the reproducibility of acoustic reflectance measurements was also tested by repeated measures analysis of variance. No effect of the day to day variability on reproducibility of acoustic parameters was found (OPJ, $p=0.6$; MPA, $p=0.8$; GLO, $p=0.5$; APA, $p=0.8$; PV, $p=0.7$).

Table 6.1 Day to day coefficient of variations for 5 different acoustic parameters in 6 subjects studied repeatedly on 8 days.

	OPJ	MPA	GLO	APA	PV
Sub 1	4.5	9.6	13.3	8.3	7.6
Sub 2	15.0	7.4	17.6	4.5	6.2
Sub 3	22.2	13.1	15.3	10.3	13.9
Sub 4	11.7	14.7	25.0	7.6	14.4
Sub 5	5.8	7.6	8.3	4.7	9.2
Sub 6	13.3	11.1	8.6	9.0	6.3
Overall CV(%)	12.1	10.6	14.7	7.4	9.6

OPJ-oropharyngeal junction area, MPA-maximum pharyngeal area, GLO-glottic area, APA-average pharyngeal area, PV-pharyngeal volume, CV-coefficient of variation.

Acoustic reflectance results in matched pairs

Out of 51 matched relative control pairs acoustic reflectance data was available in 44 relatives and 46 controls. Acoustic reflectance could not be performed on all subjects due to occassional reflectometer malfunction and the inability of some subjects to come to the sleep laboratory again for these measurements to be taken.

Results of acoustic reflectance were available in 40 matched relative control pairs (table 6.2). There were significant differences between groups in total pharyngeal volume and glottic cross sectional area but not in other variables measured.

Table 6.2 Acoustic reflectance results in 40 matched pairs.

Parameter	Relatives	Controls	P
Pharyngeal volume(cc)	19 SEM 1	23 SEM 1	0.01
Glottic area(cm^2)	1.7 SEM 0.1	1.9 SEM 0.1	0.05
Oropharyngeal junction area(cm^2)	1.7 SEM 0.1	1.8 SEM 0.1	0.9
Maximum pharyngeal area(cm^2)	2.7 SEM 0.1	2.9 SEM 0.1	0.2
Average pharyngeal area(cm^2)	2.2 SEM 0.1	2.3 SEM 0.1	0.5

Lateral cephalometry results in matched pairs

Lateral cephalometry was performed in both relatives and controls in erect position using a cephalostat and the standard protocol described in chapter 3. The standard bony and soft tissue landmarks identified and dimensions measured were the same as in pilot study.

Out of 51 matched relative control pairs, 42 relatives and 41 controls underwent cephalometric examination while the rest refused this radiological procedure.

Data from cephalometry was available in 36 matched relative control pairs. The relatives had retroposed maxillae and mandibles with shorter mandibles and longer soft palates with wider uvulae (fig 6.3, table 6.3).

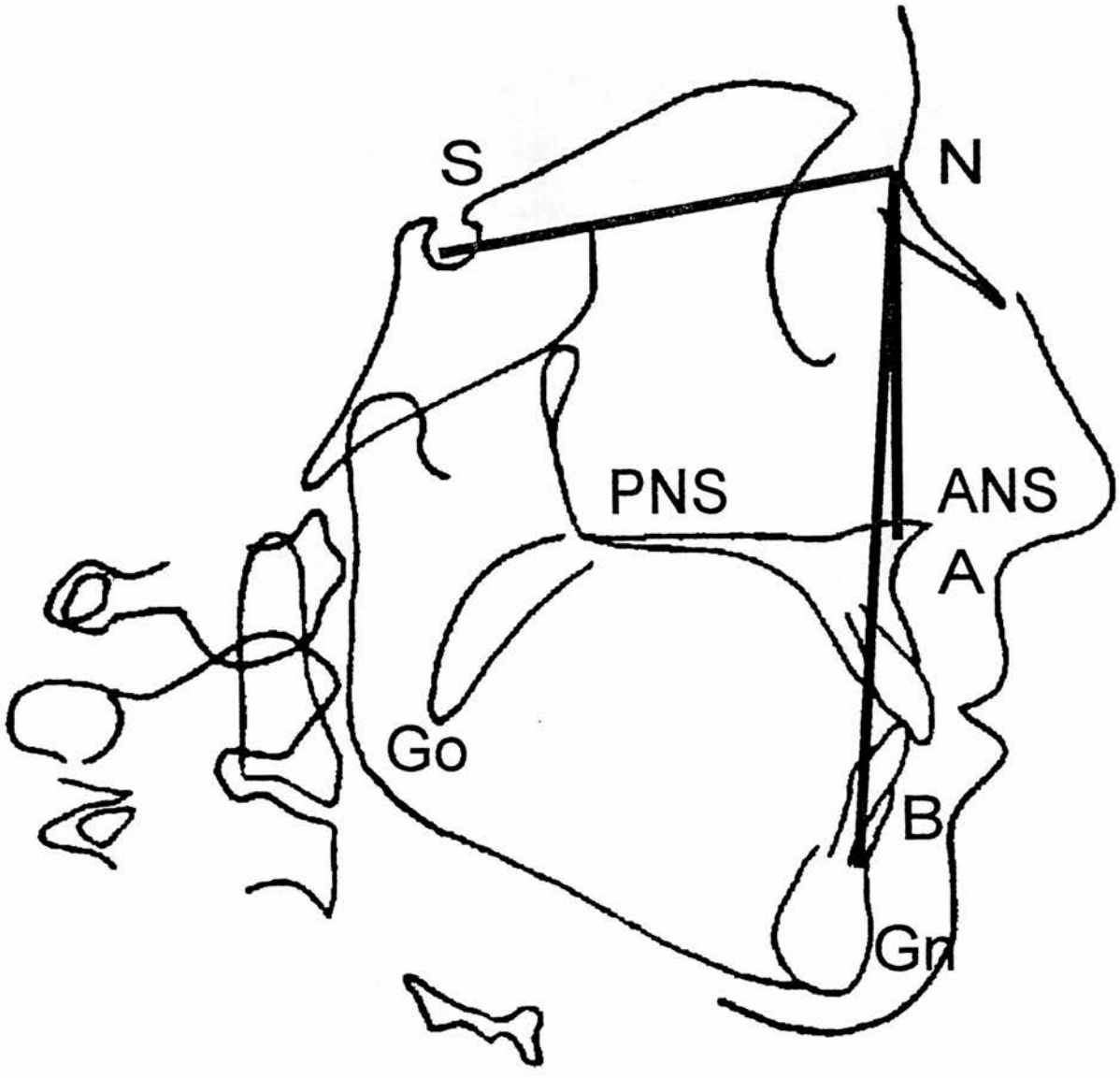

Fig 6.3 Cephalometric differences between relatives and controls

The cephalometric measurements which were not significantly different between relatives and controls are given in table 6.4.

Table 6.3 Cephalometric differences between relatives and controls.

Parameter	Relatives	Controls	P
Go-Gn(mm)	84 SEM 1	87 SEM 1	0.03
PNS-PhW(mm)	29 SEM 1	32 SEM 1	0.02
S-N-A(deg)	81 SEM 1	86 SEM 1	<0.0001
S-N-B(deg)	78 SEM 1	82 SEM 1	<0.0001
UL(mm)	45 SEM 1	43 SEM 1	0.03
UW(mm)	12 SEM 0.4	10 SEM 0.3	<0.0001

Table 6.4 Cephalometric measurements which were not significantly different between relatives and controls

Parameter	Relatives	Controls	P
ANS-PNS(mm)	41 SEM 1	42 SEM 1	0.5
S-Go(mm)	85 SEM 3	89 SEM 1	0.2
Go-H(mm)	45 SEM 1	44 SEM 1	0.7
H-MP(mm)	24 SEM 1	23 SEM 1	0.2
H-Ar(mm)	85 SEM 2	87 SEM 2	0.2
Go-PhW(mm)	6 SEM 1	5 SEM 1	0.5
Go-Ar(mm)	44 SEM 2	47 SEM 2	0.1
UP-PhW(mm)	14 SEM 1	15 SEM 1	0.3
PAS(mm)	11 SEM 1	12 SEM 1	0.4
UT-PhW(mm)	10 SEM 1	11 SEM 1	0.2
H-PhW(mm)	36 SEM 1	37 SEM 1	0.4
TB-PhW(mm)	10 SEM 1	11 SEM 1	0.6
PNS-Aat(mm)	38 SEM 1	39 SEM 1	0.6
Triangle(mm^2)	1412 SEM 105	1512 SEM 86	0.5
Go-Ga-H(deg)	27 SEM 1	25 SEM 1	0.2
Mand. angle(deg)	119 SEM 1	117 SEM 1	0.07
Neck angle(deg)	17 SEM 1	15 SEM 1	0.4
N-S-Ba(deg)	146 SEM 1	144 SEM 1	0.2
Gn-Go-Aat(deg)	121 SEM 2	121 SEM 1	0.7
Gn-Go-Ba(deg)	137 SEM 1	136 SEM 1	0.7
A-N-B(deg)	3 SEM 0.4	4 SEM 0.4	0.2

Abbreviations as explained in previous chapters.

Correlation of A+H/hour of sleep with cephalometry

To identify the subset of cephalometric variables that are most useful for predicting the number of A+H/hour of sleep, a stepwise multiple linear regression analysis was performed in 83 subjects (42 relatives) on whom cephalometric data was available. All 83 subjects were from the 51 matched pairs. In this sample UW ($p<0.0001$), S-Go ($p<0.0001$), PNS-Aat ($p=0.003$) and triangle area ($p=0.01$) were found to be most useful variables, in decreasing order of importance, explaining much of the variability in A+H/hour of sleep. Stepwise entry of UW, S-Go, PNS-Aat and triangle area in this order to the analysis accounted for 10%, 23%, 29% and 34% of the variation in A+H/hour of sleep as second, third and finally all four variables were entered into the model.

The final equation, explaining 34% of the variation in A+H/hour of sleep, was:

A+H/hr of sleep= 64.1 + 2.9(UW) - 0.7(S-Go) - 1(PNS-Aat) + 0.008(triangle).

Normative cephalometric data in controls

Table 6.5 gives normative lateral cephalometric data in erect posture in 24 male and 17 female control subjects who underwent cephalometric examination.

Table 6.5 Normative lateral cephalometry data.

	MALE		FEMALE	
Parameter	Mean	95% CI	Mean	95% CI
n	24		17	
Age (years)	35	22-58	29	23-42
BMI (kg/m^2)	26	20.5-32.7	22	18.5-23.9
ANS-PNS(mm)	42	33-61	40	32-58
Go-Gn(mm)	88	77-98	84	77-95
S-Go(mm)	93	81-108	82	75-88
Go-H(mm)	49	39-63	38	25-50
H-MP(mm)	26	15-37	20	9-32
H-Ar(mm)	93	72-115	78	67-93
Go-PhW(mm)	4	-8-14	5	0-15
Go-Ar(mm)	47	32-63	44	34-56
UP-PhW(mm)	15	4-26	15	9-23
UL(mm)	44	37-51	42	34-51
UW(mm)	11	7-13	9	6-13
PAS(mm)	12	8-21	12	8-21
UT-PhW(mm)	11	3-21	10	6-15
H-PhW(mm)	39	27-48	32	28-35
PNS-PhW(mm)	32	27-49	32	22-41
TB-PhW(mm)	11	3-25	10	6-17
PNS-Aat(mm)	38	32-44	39	34-45
Triangle(mm^3)	1588	546-3040	1427	688-2031
Go-Gn-H(deg)	29	17-45	21	11-32
S-N-A(deg)	86	78-94	85	79-93
S-N-B(deg)	83	76-89	81	75-89
A-N-B(deg)	3	-3-8	4	-2-7
Mand. angle(deg)	118	106-131	115	103-131
Neck angle(deg)	16	5-32	16	4-23
N-S-Ba(deg)	141	130-150	147	144-156
Gn-Go-Aat(deg)	119	111-134	122	110-145
Gn-Go-Ba(deg)	136	125-155	136	125-153

The sex differences in cephalometric variables are given in table 6.6. These indicate that men have bigger mandibles (Go-Gn, S-Go), lower hyoid bones (Go-H, H-MP, H-Ar, Go-Ga-H angle), more acute cranial flexure (N-S-Ba angle) and wider uvulae (UW) than women.

Table 6.6 Gender differences in cephalometric variables

Parameter	Men n=24	Women n=17	P
ANS-PNS(mm)	42 SEM 1	40 SEM 2	0.3
Go-Gn(mm)	88 SEM 1	84 SEM 1	0.008*
S-Go(mm)	94 SEM 1	82 SEM 1	<0.0001*
Go-H(mm)	48 SEM 1	38 SEM 1	<0.0001*
H-MP(mm)	25 SEM 1	20 SEM 2	0.02*
H-Ar(mm)	93 SEM 2	78 SEM 2	<0.0001*
Go-PhW(mm)	4 SEM 1	5 SEM 1	0.6
Go-Ar(mm)	48 SEM 2	44 SEM 2	0.2
UP-PhW(mm)	15 SEM 1	15 SEM 1	0.5
UL(mm)	44 SEM 1	41 SEM 1	0.08
UW(mm)	11 SEM 0.5	9 SEM 0.5	0.003*
PAS(mm)	12 SEM 1	12 SEM 1	0.5
UT-PhW(mm)	11 SEM 1	10 SEM 1	0.5
H-PhW(mm)	39 SEM 1	32 SEM 1	<0.0001*
PNS-PhW(mm)	32 SEM 1	32 SEM 1	0.9
TB-PhW(mm)	11 SEM 1	10 SEM 1	0.5
PNS-Aat(mm)	38 SEM 1	39 SEM 1	0.6
Triangle(mm^2)	1588 SEM 114	1427 SEM 91	0.3
Go-Gn-H(deg)	28 SEM 2	21 SEM 2	0.004*
S-N-A(deg)	86 SEM 1	85 SEM 1	0.6
S-N-B(deg)	83 SEM 1	81 SEM 1	0.3
A-N-B(deg)	3 SEM 0.5	4 SEM 0.6	0.3
Mand. angle(deg)	118 SEM 1	115 SEM 2	0.2
Neck angle(deg)	15 SEM 2	16 SEM 1	0.6
N-S-Ba(deg)	141 SEM 1	147 SEM 1	<0.0001*
Gn-Go-Aat(deg)	119 SEM 1	122 SEM 2	0.3
Gn-Go-Ba(deg)	135 SEM 2	136 SEM 1	0.7

* indicates results significant at $p<0.05$

CHAPTER 7

RELATIONSHIP BETWEEN ADULT SAHS AND SIDS

Relationship between adult SAHS and the Sudden Infant Death Syndrome (SIDS).

This part of the study was undertaken to find whether the incidence of unexpected infant deaths is higher in families having adults with SAHS in comparision with control families. A secondary aim was to find possible differences in facial morphology between adults in families having both SIDS and adult SAHS and in families having only adult SAHS when compared with matched adults from control families.

Methods

From the first degree relatives of all SAHS patients recruited in the study (as described in the 'patient recruitment' section of chapter 4) one relative from each SAHS family was selected at random. This relative and its matched control were requested to complete another questionnaire enquiring 'Were there any unexpected infant deaths under one year of age' in upto 4 generations in each family and what the cause of death was, if known. The relative and the control approached were also asked to supply information on the number of family members considered in each generation in question. For families reporting unexpected infant deaths in any generation, whereever available, details of the infant's age at the time of death, its sex, mother's age at the time of infant death, time of the the year the death occured,

infant's birth weight and gestational maturity were also enquired. Questions as to whether the mother received normal medical care during pregnancy, whether anyone in the household was a current smoker, whether it was a multiple pregnancy, whether the baby was breastfed and received up to date immunizations, whether the parents were employed and whether the mother took addictive unprescribed drugs during pregnancy were also asked.

The index relatives approached from the SAHS families and their matched controls from the control families underwent lateral cephalometry as described in chapter 3.

RESULTS

As discussed in chapter 5, 38 SAHS patients provided first degree relatives for sleep studies. These 38 SAHS families along with 38 control families were included in the questionnaire survey for unexpected infant deaths. One index relative from each of the 38 SAHS families with a matched control participated in this survey.

All the families came from Scotland. The index family members (21 males in both groups), answering the questionnaire and undergoing cephalometry, were matched for age (SAHS families 37 SEM 2 vs control families 35 SEM 2 years; $p=0.2$) and body mass index (SAHS families 24.7 SEM 0.6 vs control families 24.5 SEM 0.6 kg/m^2; $p=0.7$). Twentynine SAHS and 35 control families returned the questionnaire (84% overall return; $p=0.1$ between

groups). On the families returning the questionnaire, information was available in 75/116 generations of SAHS families compared to 92/140 generations in the control families ($p=0.9$). The total number of family members covered in 29 SAHS and 35 control families were 352 and 408 respectively. The average number of family members covered in both the family types were similar (SAHS families 12 SEM 0.5 vs control families 12 SEM 0.5; $p=0.8$).

Of a total of 10 deaths reported in SAHS families, 2 were allegedly due to severe pneumonia and congenital heart disease. One death was reported in a control family due to rhesus incompatibility. Thus, there were 8 unexpected and unexplained infant deaths in 6 SAHS families, and none in the control families (8 infant deaths in 29 SAHS families vs none in 35 control families, $p<0.02$). Looking at the same data from another angle, 8 infant deaths were reported out of 352 SAHS family members compared with none out of 408 control family members ($p<0.01$).

Table 7.1 gives the known details about these 8 infants for whom no cause of death was identified.

Table 7.1 Details of unexpected infant deaths in SAHS families

SAHS family 1. Male infant from single birth died suddenly 6 days after birth. Mother was 27 at the time of infant death, did not receive normal antenatal care, was a current smoker, did not breast feed the infant and did not take any unprescribed drugs during pregnancy.

SAHS family 2. Male infant of twin pregnancy died suddenly 15 days after birth. Mother was 33 at the time of infant death, breast fed the infant and did not take any unprescribed drugs during pregnancy.

SAHS family 3. Male infant from single birth died suddenly under one year age. Exact age at death and other details unknown.

SAHS family 4. Male infant from single birth died suddenly under one year of age. Mother was 38 at the time of infant death, received normal antenatal care during pregnancy and was a current smoker. Exact details unknown.

SAHS family 5. Two female infants from two separate single births both died suddenly within a few days after birth. Mother was in her late thirties and was a current smoker. No other details available.

SAHS family 6. Two twin infants of unknown sex both died suddenly under one year of age. No other details available.

Matched cephalometric data was available in 23 out of 38 relative-control pairs surveyed. Table 7.2 lists the significant differences between these groups.

Table 7.2 Significant cephalometric differences between adult members from 23 SAHS and 23 control families

Parameter	SAHS family	Control family	P
S-N-A(deg)	81 SEM 1	87 SEM 1	<0.0001
S-N-B(deg)	78 SEM 1	83 SEM 1	0.001
PNS-PhW(mm)	29 SEM 1	32 SEM 1	0.03
UW(mm)	13 SEM 0.5	10 SEM 0.4	0.001

Abbreviations as explained in previous chapters

Cephalometric data was available in 4 index subjects from the 6 SAHS families reporting unexpected infant deaths in and 4 matched index subjects from the control families. The only cephalometric parameter significantly different between these 4 SIDS families and control families was the S-N-A angle (SIDS families 82 SEM 2 vs control families 91 SEM 1 degrees; p=0.04).

Conclusions and Discussion

This part of the study suggests that there may be an increased risk of unexpected infant death in families having at least one adult with SAHS. It also showed cephalometric differences (retropositioned maxilla) between adult subjects in SAHS families having unexpected infant deaths when compared to matched controls.

To avoid the likelihood of including possible ambigious responses in the data, this study did not include cases of near miss SIDS. These results however are compatible with a preliminary report in which 6 cases of SIDS or near miss SIDS were identified in 52 SAHS families as compared to 1 instance of SIDS in 44 control families (Ferrette V et al, 1992). In that study, retrognathia tended to be more prominent in index SAHS patients from SIDS families than in other members of the cohort.

Numerous previous studies have linked sudden infant death with abnormal breathing during sleep. Kahn A et al, 1992, reported that SIDS infants have more numerous and

prolonged obstructive and mixed but not more central apnoeas than control infants. SIDS infants have been demonstrated to have fewer short central apnoeas than controls and this difference between SIDS and control infants has been found to exist during the second month of life which is just before the period of maximal risk for SIDS (Schechtman VL et al, 1991). Obstructive sleep apnoeas in SIDS and near miss SIDS infants have been associated with neuromuscular as well as with bony and soft tissue abnormalities of the upper airways (Tonkins S, 1975, Siebert JR et al, 1991) resulting in these infants having smaller upper airways which could be inherited (Guilleminault C et al, 1986b). As SIDS infants, like adult SAHS patients, have abnormal breathing during sleep, abnormal craniofacial architecture and familial aggregation (Peterson DR et al, 1980, Oren J et al, 1987, Beal SM et al, 1988) it is possible that SIDS and adult SAHS are different manifestations of a common underlying abnormality which expresses as narrowed upper airways. Upper airway narrowing, due to inherited skeletal differences in the facial anatomy, may then be responsible for abnormal breathing during sleep in both conditions.

Other investigators have questioned the role of apnoea as a common part of the initial sequence of events leading to death or near death events in infants (Southall DP, 1988). Recording physiological signals during unexplained near miss SIDS events in 77 infants and

children, Samuels MP et al, 1993, identified different mechanisms for these events. These included deliberate suffocation by a parent, hypoxaemia induced by convulsions, fabrication of history and data and severe idiopathic hypoxaemia. Further analysis of the data by Poets CF et al, 1993, confirmed prolonged severe hypoxaemia of unknown cause as an initial step in many such infants with subsequent and secondary bradycardia and asphyxic apnoea.

As in any retrospective survey, the causes of death in this study have been difficult to verify. Information from autopsy, a prerequisite for the diagnosis of SIDS, was not available in any case. The generations surveyed sometimes went back to the turn of the century and very limited, sketchy information was available. This long time span inevitably led to the families forgetting considerable information regarding the circumstances surrounding these deaths. The problem is compounded by the fact that often the immediate family members of the infant in question are themselves now dead or unavailable for confirmation of the event. The information in many cases has simply been handed down the generations in the family with the accompaning possibility of getting distorted with the passage of time.

In order to obtain as much information as possible, the families were asked to provide details of unexpected infant deaths due to all causes. The three cases in whom

the cause of death seemed reasonably certain were excluded from the analysis. As the term "SIDS" came into general usage and was agreed as an acceptable cause of death only approximately 30 years back, it was specifically not mentioned in the questionnaire which simply enquired about unexpected infant deaths.

The vast majority of SIDS deaths occur between 2-6 months of age (Froggat P et al, 1968). In some of the families in this study, the infant deaths occured a few days after birth and it may be argued that these may not be cases of true 'SIDS'. However 4% of the SIDS deaths occur under one month of age (Beckwith JB, 1973). Furthermore even if these deaths are not true SIDS, they are still significant in their own right as no similar deaths were reported by the control families whatsoever.

It was attempted to minimise the possible regional geographical bias in this study by considering only those families which came from Scotland. A bias from the possible different socioeconomic status of the SAHS versus control families was difficult to avoid. Though the SAHS families were from all over Scotland and thereby presumably encompassed all social classes, the index control subjects were from relatively lower socioeconomic strata (as judged by their residential postcode). This would therefore bias against the positive results of this study and make the findings even more remarkable.

These results do not simply reflect increased fertility rate or family size in SAHS as compared to control families. The total number of family members covered in the survey and the average number of members per family were similar in both SAHS and control families.

Further studies are required to follow up SAHS families on a long term prospective basis to determine the incidence of unexpected infant deaths in these families. Infants from SAHS families need to be studied by polysomnography to find whether they have more abnormal breathing during sleep than matched infants from control families. Likewise, adult members of the families having sudden infant death cases need to be studied to establish a firm link between these conditions.

CHAPTER 8

SIGNIFICANCE AND CONCLUSIONS

The main finding of these family studies is that SAHS is familial. The case control study shows that the first degree relatives of non obese SAHS patients have more sleep related symptoms, more abnormal breathing during sleep, greater sleep disruption, different sleep architecture and more oxygen desaturations during sleep than the matched controls. In addition, the first degree relatives of non obese SAHS patients have smaller upper airways and a different craniofacial morphology than matched controls. The studies further show a higher incidence of sudden unexplained infant deaths in families having adult members with SAHS as compared with control families.

Limitations of the study

1. Exclusion criteria

In order to avoid restudying the familial nature of obesity, relatives of only 'non obese' patients with SAHS were studied. The direct methods of quantitating the proportion of adipose tissue like body density, total body potassium measurements and isotope dilution methods are unsuitable for routine use. An indirect way of estimating adiposity is skin fold thickness measurements with triceps and subscapular skin folds being used most commonly. The correlation between hydrostatic and skin fold thickness body fat measurements has been found to be

0.84 (Revicki DA et al, 1986). However, skinfold thickness is not a totally relaible measure of obesity because of considerable variation in fat deposits in different body sites (McLaren DS et al, 1965). There is also some question whether skinfold thickness is more closely related to laboratory estimates of body fat mass than combinations of weight and height (Dugdale AE et al, 1979). Moreover, the utility of skinfold thickness measurements in large epidemiological studies remains to be demonstrated.

For these reasons, because of its ease of use and familiarity, body mass index (BMI) was used as an estimate of body adiposity. Though both Quetelet index ie, wt/ht^2 (Quetelet LA, 1871) and Benn index ie, wt/ht^p (with the exponent value of p being regression coefficient of weight on height x mean height/mean weight of the sample; Benn RT, 1971) show similar correlation with hydrostatic determination of body fat (0.7) and correlate minimally with height and maximally with weight (Revicki DA et al, 1986) only the Quetelet index was used as BMI in these studies. However, BMI is not an ideal measure of adiposity as it is unable to distinguish between adiposity, muscularity and oedema.

The cutoff point of 30 kg/m^2 was based on the classification of obesity by Garrow JS, 1981, classifying individuals of both sexes with a BMI (kg/m^2) of 20-24.5 as normal, 25-29.9 as having grade 1 obesity, 30-40 as

having grade 2 obesity and >40 as grade 3 obesity. These grades are based on the relationship of obesity to mortality which rises significantly with grade 2 obesity onwards (Garrow JS, 1981). Garrow estimates that over 4% of the British population has a BMI of over 30 kg/m^2. Six percent of adult males and 8% of adult females in Britain were found to have a BMI of over 30 kg/m^2 and were classified in another study as obese (Rosenbaum S et al, 1985).

Since the initial description (Whyte KF et al, 1989) of about 85% of SAHS patients having a BMI of >30 kg/m^2, this syndrome has been increasingly recognised in the non obese. This study found that less than half of the SAHS patients had a BMI of >30 kg/m^2 and therefore although the conclusions from these studies cannot be extrapolated to all SAHS patients, the familial factors found are applicable to a significant proportion of SAHS patients.

2. Incomplete recruitment

In the case controlled study, not all the 91 relatives of 32 participating SAHS patients underwent sleep studies. The main reason for this was financial as each relative control pair having overnight sleep studies and related investigations currently costs approximately £1000. Of the 108 total relatives, the first 51 underwent sleep studies and sleep questionnaire data was obtained on 91 (84%). The 51 relatives who underwent sleep studies were no different in terms of any sleep symptom from the 40

who were not sleep studied. Indeed, the 51 relatives who had sleep studies were younger and consumed less alcohol and fewer cigarettes and might therefore be expected to show less abnormal breathing during sleep than the 40 who were not studied.

Twenty four of these 40 unmatched relatives underwent sleep studies and were found to have a similar breathing pattern (median 11 A+H/hr of sleep) and arousals (median 34/hr of sleep) to the 51 matched relatives. Moreover, there were no differences between these 24 and the 51 relatives in any of the acoustic reflectance measurements or cephalometric results. One can therefore be confident of the conclusions that the relatives of SAHS patients have more sleep symptoms and more abnormal breathing during sleep than their matched controls.

Sleep symptom questionnaire

The results of the questionnaire survey are consistent with a previously reported symptom questionnaire study (Redline S et al, 1992a) describing more daytime sleepiness and apnoeas in relatives of patients with SAHS. Sleep studies were not performed in that study and SAHS patients were obese with a mean (SD) BMI of 37 (2) kg/m^2. However, the increased frequency of reported witnessed apnoeas remained when adjustment was attempted for the body mass of the relatives.

As in that study, a reporting bias in the sleep symptom

questionnaire data due to the possibility of relatives being more aware of symptoms than controls cannot be excluded. However, this possible bias would not account for the objective differences in sleep study and upper airway measurement results obtained in this study.

Polysomnography

The sleep study results of this study are compatible with a preliminary report that there is increased abnormal breathing in the families of patients with SAHS (Redline et al, 1992b). A limited sleep study was performed in unselected SAHS patients and their first degree relatives. Familial risk and black race were found to be important determinants of abnormal breathing during sleep in younger subjects with odds ratios of 10.8 and 10.3 respectively.

This study, in addition, reports normative data on sleep, arousals and sleep related breathing disturbance in different groups of control subjects.

Acoustic reflectance

Due to methodological difficulties, upper airway calibre cannot be measured by acoustic reflectance through the nasal route. As 50% patients have upper airway collapse at the level of soft palate (Hudgel DW et al, 1988) measurements of retropalatal areas is clearly important and this region cannot be accessed via the oral route used in this study.

Cephalometry

The cephalometric analysis in this study indicate that the relatives of thin SAHS patients have retroposed maxillae and mandibles, shorter mandibles, longer soft palates and wider uvulae than matched controls. All these observed differences would predispose to upper airway narrowing and SAHS patients have narrowed upper airways even in the awake state (Schwab RJ et al, 1993). Likewise differences in the gonion-gnathion-hyoid angle between affected and unaffected relatives were found in the pilot study indicating a lower positioned hyoid bone in the affected relatives. This would predispose the affected relatives to retroglossal airway narrowing. Both these studies do not prove that the differences in bony or soft tissue structures cause abnormal breathing during sleep.

The soft tissue abnormalities observed could represent the fundamental inherited defect in non obese SAHS patients with abnormal breathing during sleep being a consequence of this abnormal soft tissue pharyngeal anatomy. A resection study (Stauffer JL et al, 1989) demonstrated that the uvula in patients with SAHS contains more muscle and fat than the uvula in control subjects, possibly contributing to pharyngeal narrowing in SAHS. This would support the notion that the inherited and primary abnormality in SAHS patients may be altered fat deposition in the upper airway. On the other

hand, the increased muscle in the uvulae could represent muscular hypertrophy in response to the increased pharyngeal airflow resistance (Stauffer JL et al, 1989) that is commonly seen in SAHS patients, both awake and asleep. Similarily the uvular enlargement observed by cephalometry may represent mucosal oedema secondary to snoring induced vibratory trauma to the uvula (Cohn M et al, 1986).

Like soft tissue abnormalities, the bony abnormalities could also be a cause or consequence of abnormal breathing during sleep. It has been demonstrated in monkeys that prolonged experimental nasal occlusion results in morphological changes in orofacial soft tissues, facial skeleton and dental occlusion. An increase in bony face height, increase in gonial angle, steeper mandibular plane and downward displacement of maxilla were commonly seen in such animals (Harvold EP et al, 1981). Although these results from the animal model cannot be directly extrapolated to our study due to a different bony facial structure in humans, it is plausible that facial remodelling can occur in humans as a result of upper airway anatomical changes in infancy.

This study has also provided normative cephalometric data relevant for upper airway measurements in both sexes in British subjects. The only data in normal subject comes from American (Cobin SE, 1955), Canadian (Popovich F et al, 1977) and Japanese (Lowe AA et al, 1985) rather

than from the British population and ethnic differences in cephalometric data cannot be ignored (Angel JL, 1976, Richardson ER, 1980).

Bhatia SN et al in 1993 published longitudinal cephalometric growth data on subjects who participated in a growth study between 1952-1993 at the King's College School of Medicine and Dentistry, London. Although they have described longitudinal profiles of cephalometric variables for the subjects who developed normal occlusion, all such data is in a sample of 15 male and 12 female subjects under 20 years of age. Moreover, the bony cephalometric landmarks recorded in their series exclude the hyoid bone so that no measurements to and from the hyoid bone are possible and the soft tissue landmarks do not include the tongue, posterior pharyngeal wall or soft palate and therefore normative data on upper airway soft tissue dimensions is missing. This is hardly surprising as their aim was not to gather normative data on upper airways but instead to establish base line orthodontic data on normal growth changes.

Many of the cephalometric landmarks taken in the growth study were different from the ones used in these family studies on SAHS. Tables 8.1 and 8.2 compare the normative cephalometric data from the growth study with the corresponding data on controls from the present case control study in both sexes. All the data from the growth study is at 19 years of age in both sexes.

Table 8.1 Some comparative cephalometric results in normal men.

Variable	Growth study subjects n=9	Our controls n=24
S-N-A(deg)	83 SD 5	86 SD 4
S-N-B(deg)	82 SD 4	83 SD 4
A-N-B(deg)	2 SD 3	3 SD 2

Table 8.2 Some comparative cephalometric results in normal women.

Variable	Growth study subjects	Our controls
	n=10	n=17
S-N-A(deg)	81 SD 5	85 SD 4
S-N-B(deg)	79 SD 5	81 SD 4
A-N-B(deg)	2 SD 2	4 SD 2

CHAPTER 9

PLANS FOR FUTURE STUDIES

These studies show that SAHS is familial but cannot determine whether or not it is inherited. The studies also show that first degree relatives of thin SAHS patients have smaller upper airways and a different craniofacial morphology than matched controls.

Relation between abnormal breathing during sleep and abnormal craniofacial architecture

Though in the family studies described in this thesis abnormal breathing during sleep was associated with cephalometric abnormalities, no conclusions regarding cause and effect can be made. This would need further studies as demonstration of a subset of patients with severe cephalometric abnormalities but mild abnormal breathing during sleep would indicate abnormal breathing to be a consequence of abnormal facial architecture.

Upper airway measurements

These family studies demonstrated that the relatives of non obese SAHS patients have differences in soft tissues of pharynx as compared to controls. Both the studies showed a thicker soft palate in many relatives. Cephalometry cannot, however, distinguish between excessive fat, muscular tissue or oedema as the cause of uvular enlargement. This issue can be resolved by magnetic resonance imaging. Demonstration that the thicker uvula in relatives of non obese SAHS patients as

compared with controls is due to fatty infiltration would indicate abnormal fat deposition as a primary inherited abnormality in SAHS. Further studies are also required to look for a difference in upper airway muscle function between relatives and control subjects.

Genetic aspects of SAHS

The two family studies in patients with SAHS described here are the very begining of a long and arduous journey. These family studies have indicated a real possibility that at least in some families SAHS may be inherited, possibly in an autosomal dominant mode. The transmission of SAHS from father to son seen in many families analysed rules out an X linked mode of transmission (recessive or dominant). The observation that over 30% of all first degree relatives studied have abnormal breathing during sleep makes an autosomal recessive mode of inheritance less likely. This is because many apparently healthy new spouses would have to be considered heterozygote carriers of the abnormal gene to explain this high prevalance of 'affected' relatives. Taking the prevalance of SAHS as 1% of the population, the heterozygote frequency for any SAHS gene in the normal population as per Hardy Weinberg Law (Hardy GH, 1908, Weinberg W, 1908) would then be approximately 20%. The presence of so many affected relatives in these families makes multifactorial inheritance less likely as well.

The problems are compounded by the diagnostic

uncertainities in many relatives studied. Relatives with A+H of less than 5 and more than 15 per hour of sleep are probably truly unaffected and affected respectively but those having 5-15 A+H/hr of sleep fall in a diagnostic grey zone. The diagnostic uncertainty in such relatives makes many families unsuitable for genetic analyses. The variable age of onset is another problem. This implies that those relatives, especially the younger ones, who are presently unaffected may develop SAHS in future and this weakens the power of many genetic analyses. Another problem is disease heterogeneity, i.e., is SAHS one or several disorders? Many of these issues need careful consideration in planning future studies.

Various kinds of studies can be performed to further explore the issue of the role of genetics in SAHS.

1. Bigger family studies

For the reasons listed above many more families of non obese SAHS patients need to be studied to arrive at reasonable conclusions on the inheritance of SAHS. More difficult, though possible, is the question of studying more members of the same families already recruited to increase the power of genetic studies. Showing a higher incidence of abnormal breathing during sleep in the second or even the third degree relatives of these SAHS patients would add weight to the importance of genetic factors.

2. Demonstrating a higher frequency of abnormal breathing during sleep in certain racial or ethnic groups and showing that this higher frequency persists when the group moves to a different environment would also support the role of genetics in SAHS.

3. Twin studies

Demonstration of a greater concordance for abnormal breathing during sleep in monozygotic twins as compared with dizygotic twins would be an evidence of genetic contribution to the disease. This is because differences between members of a monozygous pair are entirely non genetic in origin whereas differences between members of a dizygous pair are due to a combination of genetic and environmental influences. Despite many limitations, twin studies are a valuable approach to the study of genetic and environmental influences on disease.

4. Adoption studies

Demonstration that abnormal breathing during sleep is more frequent among the biological parents of SAHS patients than among their adoptive parents and that it is equally prevalant among the biological and adoptive parents of control subjects would support the role of genetic factors in SAHS.

However these lines of investigation are at best indicative of genetic predisposition to SAHS but give no clues to the nature or number of genes involved.

Molecular genetics techniques will need to be applied to begin systematic searches of the genome for predisposing genetic loci. These techniques are-

1. Genetic linkage studies

These studies need to demonstrate a linkage and hence the genetic distance between a marker locus and the presumptive locus for SAHS gene. These studies need families having both affected and unaffected relatives through at least two generations. The probability of alleles at the marker locus cosegregating with the alleles at presumptive SAHS locus because the loci are close together on the same chromosome is compared to the probability that this has happened by chance alone.

Affected sibling pair analysis is a robust screening tool which makes no assumptions about the mode of inheritance of SAHS. This would involve noting the concordance of abnormal breathing during sleep and a marker system in multiple sets of pairs of affected siblings.

No candidate gene(s) conferring suscepitibility to SAHS has so far been identified. Although the inherited defect in non obese SAHS patients may be a defective craniofacial bony architecture, the genes coding for facial structure are unknown and may probably be many. This hampers the candidate gene linkage analysis. If such a gene is identified in future and provided that informative polymorphisms are found in or around it, its cosegregation with SAHS can be tested. Absence of a

candidate gene also makes mutation analysis impossible.

2. Genomic mismatch scanning

This procedure maps all the regions of identity by descent (inherited from a common recent ancestor) between two affected relative pairs and discards other family members from the analysis. This method may be particularly useful in SAHS as the penetrance of SAHS allele may be age dependent. Determining where on the genetic map a pair of affected relatives have inherited identical sequences from a common source and combining these identity by descent maps from multiple pairs of similarly affected relatives can create a composite map. This composite map can then be searched for loci where genotypic concordance between affected relatives occur more frequently than would be expected by chance. With a sufficiently large number of affected relative pairs such an analysis can reveal the position of genes that account even for a slight fraction of susceptibility to SAHS.

3. Disease association studies

Though the association of SAHS with antigens of HLA complex has already been reported from Japan, further similar studies will confirm the association a particular allelle with SAHS. This will be of practical value in estimating the relative risk of developing SAHS in the presence of a specific marker allelle.

The available data suggests that in Japanese population,

expressed as a relative risk, the antigen A-2 confers a suscepitibility to the development of SAHS that is 6.4 times that in the general population. This HLA association is particularly interesting as it is known that genes of importance in skeletal growth and development are located in the region of the major histocompatibility complex (Carpenter CB, 1991). Although association does not necessarily imply linkage and despite a strong association the disease gene can be present anywhere on the genome, it is logical to search for any putative SAHS gene linked to the HLA locus present on the short arm of chromosome 6. Alternatively the association might be the result of linkage disequlibrium with HLA-A2 locus genetically linked to as yet undiscovered suscepitibility locus.

It is hoped that understanding SAHS at a molecular genetic level will help in the treatment of the disease in future.

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LIST OF ABBREVIATIONS

A+H:	Apnoeas plus Hypopnoeas(/hr: per hour of sleep)
Aat:	Anterior tubercle of atlas
ADC:	Analogue to Digital Converter
ANS:	Anterior Nasal Spine
APA:	Average Pharyngeal Area
Ar:	Articulare
Ba:	Basion
BMI:	Body mass Index
CI:	Confidence Interval
CO2:	Carbon di oxide
CPAP:	Continuous Positive Airway Pressure
CV:	Coefficient of Variation
DAC:	Digital to Analogue Converter
Desats:	Oxyhemoglobin Desaturations
FRC:	Functional Residual Capacity
GLO:	Glottis and its cross sectional area
Gn:	Gnathion
Go:	Gonion
H:	Hyoid
HLA:	Human Leucocyte Antigen
MP:	Mandibular Plane
MPA:	Maximum Pharyngeal Area
MRI:	Magnetic Resonance Imaging
N:	Nasion
NREM:	Non Rapid Eye Movement Sleep
O2:	Oxygen
OPJ:	Oropharyngeal Junction and its cross sectional area
Pa:	Pascal
PAS:	Posterior Air Space
PhW:	Posterior pharyngeal wall
PNS:	Posterior Nasal Spine
PV:	Pharyngeal Volume
REM:	Rapid Eye Movement Sleep
REM LAT:	REM sleep Onset latency
S:	Sella turcica
SAHS:	Sleep Apnoea/Hypopnoea Syndrome
SaO2:	Arterial Oxygen Saturation
SD:	Standard Deviation
SEI:	Sleep Efficiency Index
SEM:	Standard Error of the Mean
SIDS:	Sudden Infant Death Syndrome
SOL:	Sleep Onset Latency
SPT:	Sleep Period Time
TB:	Tongue Base
TIB:	Time in Bed
TST:	Total Sleep Time
UL:	Uvula Length
UP:	Uvula Protrusion
UT:	Uvula tip
UW:	Uvula Width

APPENDIX

SELECTED RAW DATA

Tables 1 to 25 in this section list selected raw data. The full original data, especially on sleep symptom questionnaire , polysomnography and cephalometry results, is too exhaustive to be given in its entirety.

Throughout the tables the age is in years, BMI in kg/m^2 and collar size is in cm. Polysomnographic variables like TST, SPT and REM LAT are in minutes. AHI is the number of apnoeas plus hypopnoeas per hour of sleep. Sleep efficiency index and lowest saturations are expressed as percentage.

Arousals throughout the pilot study and in table 8 are as per Cheshire et al, 1992. The arousal data in tables 10 and 15 is as per different definitions which are fully explained in the main text.

R2%, R3%, R4%, C2%, C3% and C4% (table 21) refer to the appropriate oxyhemoglobin desaturation data in relatives and controls.

For most questionnaire data "Y" refers to Yes, "N" to No and "NR" to Not Recorded. Alcohol consumption is in units of absolute alcohol per week. Current cigarette smokers are listed as "C", ex smokers as "EX" and subjects who never smoked as "N" under the appropriate headings. EDS refers to excessive daytime sleepiness.

Cephalometric distances are in mm, angles in degrees.

Acoustic reflectance areas are in cm^2 and pharyngeal volume in cm^3.

Table 1: Details of index SAHS patients in pilot study

PATIENT	AGE	SEX	BMI	AHI	AROUSALS	COLLAR SIZE
D McFadyen	37.00	M	28.89	27.90	25.90	41.91
O Docherty	47.00	M	29.52	55.70	25.80	43.18
J O'Boyle	56.00	M	27.00	70.00	16.20	40.64
A Johnston	52.00	M	26.35	50.20	11.90	39.37
T Black	33.00	M	24.18	32.00	20.00	39.37
D Birse	52.00	M	27.62	58.10	32.30	39.37
G Steele	45.00	M	28.30	50.50	24.80	41.91
A Kempsley	48.00	M	29.02	20.40	10.00	40.64
J McLeod	73.00	M	25.69	57.40	18.60	40.64
G Rattray	51.00	M	24.43	31.00	10.50	39.37
P Hocken	52.00	M	29.20	55.30	20.90	43.18
W Gosling	59.00	M	27.70	16.50	10.50	41.91
D Muirhead	56.00	M	26.23	16.60	10.00	40.64
P O'Hagan	62.00	M	28.89	45.40	13.60	44.45
M Renwick	70.00	F	28.56	26.50	9.80	
W Dickson	54.00	M	27.77	76.20	20.30	39.37
N Cuthill	48.00	F	26.63	17.80	30.30	
W Mabberley	66.00	M	26.74	58.00	27.00	39.37
O Smart	61.00	F	26.56	17.00	21.70	
K Laycock	69.00	M	25.64	17.00	28.10	43.18

Table 2: Index SAHS patients providing relatives for pilot study

PATIENT	AGE	SEX	BMI	AHI	AROUSALS	COLLAR SIZ
D McFadyen	37.00	M	28.89	27.90	25.90	41.91
O Docherty	47.00	M	29.52	55.70	25.80	43.18
J O'Boyle	56.00	M	27.00	70.00	16.20	40.64
A Johnston	52.00	M	26.35	50.20	11.90	39.37
T Black	33.00	M	24.18	32.00	20.00	39.37
D Birse	52.00	M	27.62	58.10	32.30	39.37
G Steele	45.00	M	28.30	50.50	24.80	41.91
A Kempsley	48.00	M	29.02	20.40	10.00	40.64
J McLeod	73.00	M	25.69	57.40	18.60	40.64
G Rattray	51.00	M	24.43	31.00	10.50	39.37
P Hocken	52.00	M	29.20	55.30	20.90	43.18
W Gosling	59.00	M	27.70	16.50	10.50	41.91
D Muirhead	56.00	M	26.23	16.60	10.00	40.64
P O'Hagan	62.00	M	28.89	45.40	13.60	44.45
M Renwick	70.00	F	28.56	26.50	9.80	
W Dickson	54.00	M	27.77	76.20	20.30	39.37
N Cuthill	48.00	F	26.63	17.80	30.30	

Table 3: Selected data-unaffected relatives, pilot study

RELATIVE	AGE	BMI	TST	SE%	AROUSAL/H	AHI	MIN SAT
G BLACK	22	23.65	309.2	78	5.8	3.7	74
V BLACK	32	21.38	343.7	83		0.9	84
C MCCABE	28	22.2	414.5	94.6	8.8	4.2	90
A HOCKEN	26	25.56	413.3	94		3.7	92
N RATTRAY	22	22.18	343.9		7.1		94
P RATTRAY	23	20.31	392.3		9	0.6	86
G KEMPSLE	25	20	370.3		9.5	0.6	85
N KEMPSLE	26	26.57	363.3		12.9	6.3	80
M WEIR	60	24.42	384.1		10.9	2.5	85
H DUFFY	32	25.42	349.6		6.2		93
J CLARK	41	23.72	392.1		10.6	3.2	95
P SNAITH	43	24.25	420.4	96	7		80
E SUTHERL	30	30.2	269.8		22		80
H WALKLIN	27	27.85	328.3		9.3	1.8	87
J ROBINSO	42	27.8	336.3	79	1.9	4.7	91
A FISHER	42	24.06	369	89	7.5	8.7	86
J STEELE	21	22.28	334.6	79	5.5	2	89
D JOHNSTO	25	21.41	322.1	88	6.3	5.7	91
L JOHNSTO	21	23.53	388.8	92	5.1	0.92	89
D MCFADYE	67	36.67	352.9	86.6	7.3	11.1	69
J MCFADYE	39	22.22	387.1	94	4.3	1.4	86
M TELFORD	39	19.4	279	64	6.7	2.8	95
A HENDERS	44	23.25	286.5	77	6.5	0.2	90
J O'HAGAN	33	19.71	347.1		15.6	1.2	90
M O'HAGAN	29	26.17	351		11.1	7.35	90
A WOOD	30	18.65	342.7	77	6.3	0	95
G BIRSE	33	22.22	283.2		8.1	1.48	90
S GOSLING	19	28.24	320.9		15.9		80
L GOSLING	28	24.38	201.1		17.9		85
E GOSLING	55	35.16			7.6		77

Table 4: Selected data-affected relatives, pilot study

RELATIVE	AGEAFF	BMIAFF	TST	SE%	AROUSAL/H	AHI	LOW SAT
T BLACK	57	28.86	293.8	89	6.5	16.8	75
B RATTRAY	48	25.87	338.7	84.3	23.6	20	78
I MCLEOD	43	28.86	370.9	80.4	16.7	18.9	81
J MCLEOD	58	27.47	352	51.7	45.4	25.9	71
K DICKSON	50	31.12	239.3	76	15.7	29.6	82
I RENWICK	40	24.93	325.1	90	7.7	22.7	90
SUS O'BOYLE	28	30.74	385.5	93	11.2	19.5	88
SEAN O'BOYLE	26	21.29	340.6	74	13	15.6	85
A O'HAGAN	28	25.62	277.2	79	8.2	18.2	85
D GOSLING	58	29.02	357.3	73.3		30.8	77

TABLE 5: Selected questionnaire data-pilot study rel.

RELATIVE	TYPE	BEDPARTNERS	APNEAS	SNORING
G BLACK	UNAFF	Y	N	N
V BLACK	UNAFF	N	N	N
C MCCABE	UNAFF	Y	N	N
A HOCKEN	UNAFF	Y	N	N
N RATTRAY	UNAFF	N	N	N
P RATTRAY	UNAFF	N	NR	N
G KEMPSLEY	UNAFF	Y	N	N
N KEMPSLEY	UNAFF	Y	N	N
M WEIR	UNAFF	N	NR	Y
H DUFFY	UNAFF	Y	N	N
J CLARK	UNAFF	N	NR	N
P SNAITH	UNAFF	Y	N	N
E SUTHERLAND	UNAFF	Y	N	N
H WALKLINGSHAW	UNAFF	Y	N	N
J ROBINSON	UNAFF	Y	N	N
A FISHER	UNAFF	Y	N	N
J STEELE	UNAFF	N	NR	N
D JOHNSTON	UNAFF	N	NR	N
L JOHNSTON	UNAFF	N	NR	N
D MCFADYEN	UNAFF	Y	N	Y
J MCFADYEN	UNAFF	Y	N	Y
M TELFORD	UNAFF	Y	N	N
A HENDERSON	UNAFF	Y	N	Y
J O'HAGAN	UNAFF	Y	N	N
M O'HAGAN	UNAFF	Y	N	Y
A WOOD	UNAFF	Y	N	N
G BIRSE	UNAFF	Y	N	N
S GOSLING	UNAFF	Y	N	N
L GOSLING	UNAFF	Y	N	N
E GOSLING	UNAFF	N	NR	N
T BLACK	AFF	Y	Y	Y
B RATTRAY	AFF	Y	Y	Y
I MCLEOD	AFF	Y	Y	N
J MCLEOD	AFF	Y	N	Y
K DICKSON	AFF	Y	N	Y
I RENWICK	AFF	Y	Y	Y
SUS O'BOYLE	AFF	N	NR	Y
SEAN O'BOYLE	AFF	N	NR	NR
A O'HAGAN	AFF	N	N	Y
D GOSLING	AFF	Y	Y	Y

Table 6: Sig. cephalometrics-supine posture, pilot study

UNAFF REL	Go-Gn-H	AFF REL	Go-Gn-H
E GOSLING	35.00	SEAN O'BOYLE	28.00
P SNAITH	19.00	SUS O'BOYLE	28.00
A WOOD	28.00	K DICKSON	27.00
S GOSLING	15.00	A O'HAGEN	34.00
L GOSLING	18.00	I RENWICK	26.00
M O'HAGAN	27.00	T BLACK	
J O'HAGAN	13.00	J MCLEOD	43.00
V BLACK	19.00	I MCLEOD	
J STEEL	11.00	B RATTRAY	27.00
M TELFORD	23.00	D GOSLING	30.00
L JOHNSTON	15.00		
G BLACK	16.00		
D JOHNSTON	19.00		
M WEIR	23.00		
A HENDERSON	19.00		
H WILKINSHAW	18.00		
E SUTHERLAND	14.00		
H DUFFY	16.00		
J CLARK	27.00		
N RATTRAY	21.00		
A HOCKEN	22.00		
C MCCABE	26.00		
A FISHER	25.00		
J MCFAYDEN	22.00		
J ROBINSON	15.00		
N KEMPSLEY	28.00		
G KEMPSLEY	23.00		
G BIRSE	27.00		
P RATTRAY	31.00		
D MCFAYDEN	24.00		

Table 7: Sig. cephalometrics-erect posture, pilot study

UNAFF REL	UW	AFF REL	UW
E GOSLING	10.00	SEAN O'BO	12.00
P SNAITH	10.00	SUS O'BOY	10.00
A WOOD		K DICKSON	14.00
S GOSLING	7.00	A O'HAGEN	11.00
L GOSLING	11.00	I RENWICK	13.00
M O'HAGAN	8.00	T BLACK	14.00
J O'HAGAN	7.00	J MCLEOD	17.00
V BLACK	8.00	I MCLEOD	14.00
J STEEL	11.00	B RATTRAY	9.00
M TELFORD	10.00	D GOSLING	13.00
L JOHNSTON	8.00		
G BLACK	8.00		
D JOHNSTON	9.00		
M WEIR	13.00		
A HENDERSON	10.00		
H WILKINSHAW	8.00		
E SUTHERLAND	13.00		
H DUFFY	12.00		
J CLARK	12.00		
N RATTRAY	12.00		
A HOCKEN	5.00		
C MCCABE	9.00		
A FISHER	13.00		
J MCFAYDEN	10.00		
J ROBINSON	9.00		
N KEMPSLEY	13.00		
G KEMPSLEY	12.00		
G BIRSE	10.00		
P RATTRAY	11.00		
D MCFAYDEN	12.00		

Table 8: Details of index SAHS patients-case control study

PATIENT	AGE	SEX	BMI	AHI	AROUSAL/H
I AITKEN	52	M	28	32	41
D FAIRWEATHER	68	M	23	32	140
J LAFFERTY	48	M	25	53	30
R DEMPSTER	61	M	27	33	
AI NAPLES	52	F	21	31	
C SILLET	42	M	26	44	18
J WILLIAMS	53	M	26	34	20
D ORROCK	61	M	29	72	48
G TAYLOR	61	M	26	28	19
C IRELAND	65	M	28	105	13
I NICHOLSON	57	M	26	53	56
R SIMPSON	57	M	27	16	36
H KERR	50	M	29	27	21
J IMRAY	59	M	29	25	22
G STEEL	45	M	28	51	25
J O'BOYLE	56	M	26	70	
A MILROY	63	M	26	76	55
W HAINING	66	M	26	24	53
M BRUNTON	34	M	24	23	25
T HAY	28	M	27	57	62
P McCONACHIE	40	M	24	20	28
C MACKAY	55	M	26	35	38
R DOCHERTY	46	M	27	20	22
D WARD	39	M	29	42	48
T HAWKINS	68	M	25	76	76
E McDONALD	71	F	29	57	89
J MUNCIE	58	M	27	32	35
D GRAY	40	M	30	19	51
S PAXTON	57	M	23	42	92
A GALL	64	M	25	120	94
H ARMOUR	49	M	26	36	64
D HEWITT	63	M	25	47	74
G BONNAR	64	M	25	65	65
A GREENAN	53	M	24	18	30
I PETTIGREW	37	M	29	19	45
R STARK	49	M	28	37	42
J McARTHUR	44	M	23	30	53
F WILSON	52	M	30	15	
A CHOPRA	33	M	26	73	87
D KELL	46	M	27	48	36
C HOPKIN	38	M	23	23	44
I SELF	45	M	30	33	49
C BARLOW	48	M	24	28	29
R SMITH	50	M	28	76	
A HAMILTON	41	M	27	18	25

TABLE 9: Questionnaire data-case control study relatives

RELATIVE	SEX	AGE	SMOKE	ALCOH	CHOK	BEDPART	APNEAS	SNORING	EDS
JD HAMILTON	M	51	C	13	N	Y	N	Y	N
B COLLINS	F	58	N	2	N	N	NR	N	N
J SCHOFIELD	F	27	N	8	N	Y	N	N	N
A IRONS	F	21	N	1	N	Y	N	N	Y
S FAIRWEATHER	F	28	EX	7	N	N	N	N	Y
DR. A IRELAND	M	68	EX	6	N	Y	N	N	N
D BOLAN	F	54	C	5	N	Y	N	Y	Y
D SIMPSON	M	45	C	13	Y	N	Y	Y	Y
A AITKEN	M	21	N	20	N	Y	N	N	Y
S WILLIAMS	F	24	N	1	N	N	NR	Y	N
D SILLET	M	41	N	17	N	Y	N	Y	Y
J SPOWART	F	30	N	1	N	Y	N	N	N
L IRELAND	M	33	EX	9	N	Y	N	N	N
Crg IRELAND	M	20	N	0	N	N	NR	N	N
K LAFFERTY	F	20	N	0	N	N	NR	N	Y
G AITKEN	M	21	N	20	N	N	NR	N	Y
B CAMPBELL	M	25	N	8	N	Y	N	N	N
F FAIRWEATHER	F	32	C	5	Y	Y	N	N	Y
D TAYLOR	F	50	C	13	N	Y	N	N	N
I TAYLOR	M	52	N	20	N	Y	N	N	N
Col IRELAND	M	36	EX	5	Y	Y	N	N	Y
Char IRELAND	M	62	EX	6.5	N	N	NR	NR	N
S WILSON	F	31	N	3	N	Y	N	N	Y
B ORROCK	M	28	C	8	N	Y	N	N	Y
GW IRELAND	M	65	EX	22.5	N	Y	N	N	Y
E MELLON	F	48	C	50	N	Y	N	Y	Y
GH KERR	M	24	N	3	Y	Y	N	N	Y
M STEELE	M	22	C	20	N	N	NR	N	Y
E IMRAY	F	22	N	14	N	N	NR	N	Y
A WOOD	F	45	C	7	N	Y	NR	Y	Y
J GALL	F	31	N	4	N	Y	N	N	Y
JE MUNCIE	M	16	N	0	N	N	NR	Y	N
M McCONACHIE	M	44	C	28	Y	N	NR	Y	N
A IRELAND	M	28	N	6	N	Y	N	N	Y
S AITKEN	F	18	N	0	N	N	NR	N	N
JA BOGIE	M	46	C	0	N	Y	N	Y	N
C BRUNTON	M	39	EX	20	N	Y	N	N	Y
D MILROY	M	29	N	12	Y	Y	Y	Y	Y
C McMICHAEL	F	32	EX	0	Y	Y	N	N	N
D McCONACHIE	M	43	N	24	N	N	NR	Y	N
K MOUNTAIN	F	43	N		N	Y	N	Y	Y
R HAY	M	31	C	27	Y	Y	N	Y	Y
K MUIR	F	33	N	1	N	Y	N	Y	N
S WALKER	F	28	N	4	N	Y	N	N	Y
S PAXTON	M	28	EX	4	N	Y	N	Y	Y
M McCAULEY	F	33	N	8	N	Y	N	N	N
S PIGGOT	F	30	C	2	N	Y	N	Y	Y
E McLAUGHLIN	F	34	N	5	N	Y	N	N	Y
D WARD	M	41	C		N	Y	N	Y	Y
J HAWKINS	M	73	EX	0	N	NR	NR	Y	Y
P TINDALL	F	44	N	2	N	Y	N	Y	N
D PAXTON	M	31	EX	6	N	Y	N	N	N
J PRYOR	F	39	N	14	N	Y	N	N	Y
J DOCHERTY	M	40	C	12	N	Y	N	N	Y

TABLE 9: continued...

C KERR	M	54	N	15	Y	Y	Y	Y	Y
M FRIEL	F	56	EX	6	N	Y	N	N	Y
Rob SELF	M	20	N	0	N	N	NR	Y	Y
M TAIT	F	59	N	4	N	Y	N	N	Y
J HEWITT	M	30	N	14	N	Y	N	Y	Y
RK SELF	M	52	C	12	N	Y	Y	Y	Y
MG BOGIE	F	74	N	3	N	Y	N	Y	Y
H CAMPBELL	F	29	C	9	N	N	NR	Y	Y
A PETTIGREW	F	62	C	1	N	Y	N	Y	N
T PETTIGREW	M	65	C	12	N	Y	Y	Y	N
N STARK	M	20	C	0	N	Y	N	Y	N
V WATSON	F	50	EX	2	N	Y	N	Y	Y
C JOHNSTON	F	38	N	3	N	Y	N	N	N
Mag BROWN	F	49	EX	11	N	Y	N	N	N
M HIGHLEY	F	47	N	0	N	NR	N	NR	Y
H ARMOUR	F	18	N	3	N	N	N	N	N
S ARMOUR	M	22	N	0	N	N	NR	N	N
T GREENAN	M	46	C	8.5	N	Y	N	N	N
J GREENAN	M	55	C	21	N	Y	N	Y	Y
T WARD	M	44	C	30	Y	Y	Y	Y	Y
J STARK	F	17	C	9	N	N	NR	Y	Y
S CRAWFORD	F	39	N	6	N	Y	N	N	N
G HAMILTON	M	37	C	14	N	Y	N	Y	Y
H DOCHERTY	M	37	C	20	N	Y	N	Y	N
J NICHOLSON	F	28	C	14	N	Y	N	N	N
J IRELAND	M	63	N	0	N	Y	N	N	N
K HOPKIN	M	68	C	0	N	Y	N	N	N
J HOPKIN	F	64	C	0	N	Y	N	N	N
S CZABANIUK	F	32	C	15	N	Y	N	N	N
G BRUNTON	M	48	C		N	Y	Y	Y	Y
J DOCHERTY	M		C	30	N	Y	N	N	N
MJ GREENAN	M	29	N	36	N	Y	N	Y	N
M McCALLUM	F	40	C	10	N	Y	N	N	Y
R WARD	M	51	C	14	N	Y	N	N	Y
R HARGIE	F	37	C	5.5	N	Y	N	Y	N
M LIDDON	F	33	N	2	N	Y	N	Y	N
M JEPHSON	F	60	C	7	N	N	NR	N	Y
N PARKES	F	73	N	6.5	N	Y	N	N	N
E WARD	F	78	N	0	N	N	NR	NR	N
C WILSON	F	76	EX	2	N	N	NR	NR	N
E DOCHERTY	F		C	20	N	N	NR	NR	Y
S CHOPRA	M	44	N	0	Y	Y	Y	Y	Y
M GALL	F	68	EX	1	N	N	NR	NR	Y
J McGREGOR	F	44	EX	20	Y	N	NR	NR	N
R KERR	F	17	N	0	N	N	NR	NR	N
W IMRAY	M	51	EX	30	N	Y	N	N	N

Table 10: Selected data on case control study relatives

RELATIVE	SEX	AGE	BMI	TST	SE%	AHI	3SECA
B COLLINS	F	58	24.97	250.5	56.8	14.90	31.52
J SCHOFIELD	F	27	22.59	346.7	79.0	6.60	26.47
A IRONS	F	21	23.93	386.0	84.8	16.17	36.01
S FAIRWEATHER	F	28	23.42	442.0	95.9	11.80	22.61
D SIMPSON	M	45	21.33	198.3	44.5	25.70	67.07
A AITKEN	M	21	22.16	334.2	80.9	3.10	28.93
S WILLIAMS	F	24	19.44	392.1	91.0	11.80	28.97
D SILLET	M	41	26.73	326.0	85.1	14.40	31.40
J SPOWART	F	30	25.14	364.6	84.4	7.70	26.17
Rob SELF	M	20	21.86	415.9	91.8	11.25	30.15
S AITKEN	F	18	22.14	321.4	86.2	2.80	29.47
K LAFFERTY	F	20	27.81	235.8	58.7	20.40	39.36
G AITKEN	M	21	25.05	294.6	81.1	2.40	38.76
GH KERR	M	24	25.92	421.5	94.7	9.40	22.50
B ORROCK	M	28	26.23	399.0	89.9	11.40	25.73
D TAYLOR	F	50	29.24	386.1	82.5	11.50	32.10
I TAYLOR	M	52	21.51	322.0	75.9	25.30	63.47
Col IRELAND	M	36	31.97	347.7	82.0	24.16	40.53
I DEMPSTER	M	46	26.79	362.2	82.1	26.70	43.00
G WILLIAMS	M	65	28.40	126.3	33.1	67.46	54.32
E IMRAY	F	22	23.95	304.6	72.5	16.40	28.39
S PAXTON	M	28	25.84	419.1	92.9	8.30	26.38
S WILSON	F	31	23.87	358.2	83.7	10.40	29.10
A WOOD	F	45	32.31	343.8	81.5	18.00	29.72
C KERR	M	54	28.28	409.5	94.3	27.99	56.95
R HAY	M	31	22.62	330.1	75.5	15.50	39.17
D McCONACHIE	M	43	29.40	336.3	75.7	58.30	81.53
C McMICHAEL	F	32	22.10	389.3	90.1	9.40	20.44
K MUIR	F	33	19.95	395.8	89.6	12.73	23.37
K MOUNTAIN	F	43	24.39	392.4	91.2	19.42	28.12
S WALKER	F	28	21.22	397.6	91.0	9.36	26.22
J HAWKINS	M	73	27.80	205.2	48.9	21.05	33.53
D MILROY	M	29	27.61	353.6	83.2	4.20	23.46
M McCAULEY	F	33	22.32	370.8	88.7	6.47	24.83
P TINDALL	F	44	23.42	351.7	84.1	16.21	32.19
J DOCHERTY	M	40	21.23	428.4	95.4	4.48	24.56
D WARD	M	41	24.98	392.4	88.2	8.87	28.65
JE MUNCIE	M	16	20.09	414.1	87.9	6.09	22.57
J BOGIE	M	46	25.66	384.6	88.2	15.60	40.24
S PIGGOT	F	30	23.42	414.5	90.3	7.40	30.05
M McCONACHIE	M	44	22.16	271.6	75.9	24.50	40.11
T PETTIGREW	M	65	23.81	310.6	74.7	16.04	37.71
S CRAWFORD	F	39	21.71	371.2	88.0	7.44	29.10
M TAIT	F	59	38.46	355.6	84.9	88.25	78.41
J STARK	F	17	18.29	361.3	86.0	5.65	22.77
A PETTIGREW	F	62	19.57	318.7	76.6	23.70	46.77
N STARK	M	20	22.28	366.5	92.3	11.30	26.30
Mag BROWN	F	49	25.91	346.3	77.5	36.04	64.33
J HEWITT	M	30	27.80	358.1	85.3	16.08	32.16
H ARMOUR	F	18	20.66	346.8	82.2	9.17	35.68
S ARMOUR	M	22	20.75	334.5	79.6	14.71	31.68
D BOLAN	F	54	26.06	335.6	84.3	9.48	34.45
M STEELE	M	22	23.25	392.7	86.3	10.24	29.57
R HAINING	F	33	23.15	346.6	81.9	2.08	30.20

Table 10: continued...

J GREENAN	M	55	27.28	325.7	78.1	8.48	41.80
E MELLON	F	48	31.44	306.9	70.6	7.43	26.28
MG BOGIE	F	74	29.76	256.2	59.6	25.29	52.64
M FRIEL	F	56	29.21	279.9	68.3	22.94	51.80
D PAXTON	M	31	26.03	290.2	63.9	15.92	48.47
C JOHNSTON	F	38	23.34	365.2	85.9	7.72	22.78
RK SELF	M	52	23.85	261.0	60.4	28.05	34.67
A IRELAND	M	28	33.74	406.1	97.2	6.65	23.29
F FAIRWEATHER	F	32		353.4	88.8	2.89	24.38
C BRUNTON	M	39	26.72	379.3	88.6	9.65	26.17
E MCLAUGHLIN	F	34	28.79	377.1	88.5	8.75	29.10
V WATSON	F	50	33.65	370.8	89.3	12.78	33.05
J HAMILTON	M	51	25.75	239.5	61.9	20.80	43.49
G HAMILTON	M	37	27.17	335.5	74.9	16.27	36.08
T WARD	M	44	28.67	352.0	86.3	10.74	35.41
C IRELAND	M	62	24.75	242.1	55.7	11.65	52.68
M HIGHLEY	F	47	25.72	351.2	79.5	11.96	26.87
H CAMPBELL	F	29	29.17	411.2	95.4	24.95	29.35
T GREENAN	M	46	27.87	353.6	84.2	9.67	24.65
B CAMPBELL	M	25	24.45	346.1	83.6	5.55	30.46
CRG IRELAND	M	20	24.61	360.0	84.9	4.33	22.93
J GALL	F	31	24.67	354.7	82.5	2.71	21.96
J PRYOR	F	39	21.93	416.2	95.5	3.32	20.25
DR A IRELAND	M	68	26.41	87.5	20.4	2.06	34.89
L IRELAND	M	33	25.60	338.3	74.4	9.58	38.12

Table 11: Desaturation data-case control study relatives

RELATIVES	Desat2%/hr	Desat3%/hr	Desat4%/hr
B.COLLINS	3.40	1.90	1.40
J.SCHOFIELD	1.80	0.80	0.30
A.IRONS	3.10	1.90	1.20
S.FAIRWEATHER	1.40	0.90	0.10
Dr.A.IRELAND	3.00	0.70	0.30
D.BOLAN	2.60	0.90	0.30
D.SIMPSON	7.10	3.90	1.00
A.AITKEN	2.50	1.70	1.00
S.WILLIAMS	0.00	0.00	0.00
D.SILLET	1.40	0.90	0.60
J SPOWART	3.10	1.10	0.70
L.IRELAND	2.10	0.90	0.60
Crg.IRELAND	6.00	3.90	1.60
S.AITKEN	1.90	1.00	0.20
K.LAFFERTY	4.90	1.10	1.00
G.AITKEN	0.80	0.20	0.20
GH.KERR	0.80	0.70	0.50
H.CAMPBELL	7.90	2.90	1.00
B ORROCK	1.70	0.40	0.10
A.IRELAND	2.40	1.10	0.60
F.FAIRWEATHER	1.00	0.40	0.40
B.CAMPBELL	2.40	1.30	0.60
D.TAYLOR	5.50	3.10	1.40
I.TAYLOR	6.70	2.70	1.10
C.IRELAND	7.00	2.20	0.80
Col.IRELAND	7.30	5.90	3.70
I.DEMPSTER	6.50	4.60	3.50
G.WILLIAMS	11.70	7.10	4.60
E.MELLON	4.10	1.10	0.30
E.IMRAY	3.60	2.10	1.30
S PAXTON	9.30	4.00	2.80
S WILSON	2.10	0.70	0.60
A WOOD	5.30	3.60	2.60
C KERR	19.70	13.00	7.70
R HAY	4.80	1.50	0.80
C BRUNTON	3.40	0.60	0.30
R HAINING			
D McCONACHIE	43.20	37.80	27.80
C McMICHAEL	8.80	7.10	2.70
K MUIR	1.80	0.80	0.50
K MOUNTAIN	8.20	6.80	1.80
S WALKER	3.40	2.20	1.50
J HAWKINS	10.00	4.60	3.00
D MILROY	3.40	1.90	0.70
M MCCAULEY	2.90	2.00	1.70
M MCCONACHIE	7.30	2.70	1.00
P TINDALL	7.20	3.90	1.20
J DOCHERTY	1.00	0.10	0.10
D WARD	0.80	0.10	0.00
J PRYOR	1.30	1.10	1.00
JE MUNCIE	1.00	0.30	0.20
J BOGIE	9.40	4.10	2.50
S PIGGOT	5.30	3.40	1.90
M.STEEL	0.40	0.10	0.00

Table 11: continued...

D PAXTON	6.80	3.30	1.70
E MCLAUGHLIN	8.70	6.20	3.70
J GALL	1.00	0.30	0.30
M FRIEL	4.00	0.90	0.30
Rob SELF	5.60	1.30	0.50
J STARK	3.40	1.40	0.90
M TAIT	32.90	22.20	16.30
J HEWITT	3.00	1.00	0.70
RK SELF	1.40	0.40	0.30
M BOGIE	6.10	1.60	0.70
A PETTIGREW	9.00	4.60	2.50
T PETTIGREW	1.90	0.60	0.30
N STARK	2.50	0.80	0.50
V WATSON	12.70	10.20	5.00
C JOHNSTON	0.10	0.10	0.10
Mag BROWN	3.20	1.60	0.90
M HIGHLEY	2.30	1.00	0.40
H ARMOUR	0.60	0.10	0.00
S ARMOUR	1.00	0.20	0.00
T WARD	3.40	2.10	1.50
J GREENAN	1.60	0.00	0.00
T GREENAN	3.90	1.90	1.60
S CRAWFORD	2.90	1.00	0.30
JD HAMILTON	2.90	1.80	0.60
G HAMILTON	4.90	2.00	0.70

Table 12: Anthropometric data-all control subjects

CTRLS	SEX	AGE	BMI
A.BELL	F	64.00	25.04
E BRYSON	F	32.00	21.22
C COLEY	F	23.00	22.10
A DARBYSHIRE	F	30.00	20.53
C.HARKESS	M	23.00	31.60
G.BAIRD	M	22.00	20.45
SA.BAIRD	F	25.00	18.52
D BARRIE	M	37.00	25.43
C BARLEE	F	28.00	23.53
HM ARNOT	M	30.00	24.07
S ARTHUR	M	30.00	23.30
J ARKLEY	F	20.00	21.91
Y AITKEN	F	26.00	26.67
G BEAN	M	23.00	22.16
S HOOI	M	25.00	24.30
R BURGASS	M	32.00	22.22
M BROWN	F	57.00	20.07
R BROWN	M	58.00	29.75
N CLARK	M	31.00	32.70
J ABERDOUR	M	34.00	23.12
R AITKEN	M	58.00	25.50
Al BROWN	F	29.00	27.90
Ang BROWN	M	28.00	22.16
Ed BURGASS	F	34.00	21.48
Y CAMERON	F	23.00	28.34
K McKENZIE	M	51.00	28.48
P CADDICK	M	29.00	21.33
R DONAGHUE	M	52.00	29.09
H ENGLEMAN	F	30.00	21.83
K STEDUL	F	26.00	22.80
C LEITH	F	23.00	23.51
MD COOPER	F	29.00	20.57
G CLABBIE	M	70.00	27.94
M BRICKELL	M	30.00	22.72
G BOYD	F	26.00	21.34
I LAURIE	F	42.00	23.92
D SKUDLAERK	M	30.00	23.15
A BOWMAN	M	34.00	22.40
C HOY	M	17.00	21.56
J.DEAS	M	63.00	27.43
J BURNS	F	23.00	24.98
K BOYD	M	29.00	23.10
W BEIRNE	M	71.00	22.10
L CHEYNE	F	33.00	21.45
Y BOWMAN	F	34.00	30.09
S CONNOLLY	F	35.00	22.66
J DALEY	F	64.00	24.59
K CLYNE	F	44.00	22.50
R DEWES	M	24.00	25.14
G CHRISTIE	F	24.00	23.08
S BERNARD	M	27.00	27.78
D ARMET	M	44.00	24.57
M CONNOLLY	M	61.00	26.51
G ASPINALL	M	66.00	28.70
A BERRY	M	67.00	34.96

Table 13: Selected questionnaire data on controls

SUBJECT	SMOKE	ALCOHL	CHOKE	BEDPART	APNEAS	SNORING	EDS
M CONNOLLY	C	10	N	N	N	Y	N
D ARMET	EX	5	N	Y	N	Y	N
G ASPINALL	C	9	N	N	N	Y	N
A BELL	N	9	N	N	NR	N	N
E BRYSON	N	15	N	Y	N	N	N
C COLEY	N	8	N	N	N	N	Y
A DARBYSHIRE	N	1	N	Y	N	N	N
J DEAS	EX	19	N	N	NR	NR	N
J DALEY	EX	23	N	N	NR	N	N
C HARKESS	N	0	N	N	NR	N	N
G BAIRD	N	8	N	Y	N	N	Y
SA BAIRD	N	4	N	Y	N	N	N
D BARRIE	EX	14	N	Y	N	N	N
C BARLEE	N	1	N	Y	N	N	N
HM ARNOT	C	30	N	Y	N	N	Y
S ARTHUR	C	0	N	Y	N	N	N
A BERRY	EX	12	N	Y	N	N	N
J ABERDOUR	N	12	N	Y	N	Y	N
C HOY	N	0	N	N	NR	N	N
S BERNARD	N	6	N	Y	N	N	Y
J ARKLEY	C	6	N	Y	N	N	N
Ang BROWN	EX	8	N	Y	N	Y	N
Alice BROWN	N	10	N	Y	N	Y	Y
P CADDICK	N	0	N	Y	N	N	Y
Edith BURGASS	N	2	N	Y	N	N	N
M BROWN	N	0	N	Y	N	N	N
G BEAN	N	26	N	Y	N	Y	Y
Y AITKEN	C		N	N	NR	NR	N
R BROWN	EX	17	N	Y	Y	Y	N
S HOOI	N	0	N	N	N	NR	N
Y BOWMAN	N	2	N	Y	N	N	Y
R BURGASS	N	8	N	Y	N	N	N
M BRICKELL	N	12	N	Y	N	N	N
A BOWMAN	N	4	N	Y	N	N	N
R DONAGHUE	N	16	N	Y	Y	Y	N
J BURNS	N	0	Y	N	NR	N	Y
Y CAMERON	N	3	N	Y	N	N	N
G CLABBIE	C	22	N	Y	N	N	N
K BOYD	N	12	N	Y	N	N	Y
W BEIRNE	EX	0	N	N	NR	N	N
R AITKEN	N	1	N	Y	N	N	Y
G BOYD	N	3	N	Y	N	N	N
D SZKUDLAREK	EX	0	N	N	NR	N	N
I LAURIE	EX	2.5	N	Y	N	Y	N
K STEDUL	N	7	N	N	NR	N	Y
H ENGLEMAN	C	5	N	Y	N	N	N
R DEWES	N	26	N	Y	N	N	Y
N CLARK	N	4.5	N	Y	N	N	N
C LEITH	C	19	N	Y	N	N	N
K McKENZIE	EX	6	N	Y	N	N	Y
Dr MD COOPER	N	3	N	N	NR	N	N
S CONNOLLY	C	2	N	Y	N	N	N
K CLYNE	N	0	N	Y	N	N	Y
L CHEYNE	N	6	N	Y	N	N	Y
G CHRISTIE	EX	10	N	Y	N	N	N

Table 14: Selected polysomnographic data on controls

CONTROL	TST	SOL	REMLat	SE%	AHI
A BELL	190.90	69.20	123.00	46.00	2.20
E BRYSON	340.10	26.00	130.20	86.50	0.90
C COLEY	274.70	22.30	121.90	61.90	0.00
A DARBYSHIRE	357.40	16.70	99.00	85.70	1.50
C HARKESS	201.80	27.20	310.20	51.70	1.20
G BAIRD	366.80	15.20	80.70	84.90	0.70
SA BAIRD	286.90	6.80	285.00	74.00	7.70
D BARRIE	325.50	35.60	96.00	78.80	2.40
C BARLEE	321.30	22.70	38.60	74.40	2.80
S ARTHUR	328.60	11.10	120.30	75.70	2.90
J ARKLEY	369.90	47.50	81.10	85.80	5.20
Y AITKEN	355.80	22.70	131.40	92.20	2.90
G BEAN	377.10	27.10	69.70	83.20	14.20
S HOOI	327.40	19.10	91.30	76.30	11.00
R BURGASS	402.10	19.20	68.00	91.60	3.90
M BROWN	358.90	30.80	178.50	81.70	7.20
R BROWN	335.40	14.70	139.80	76.40	13.20
N CLARK	407.90	3.90	81.50	93.80	5.88
J ABERDOUR	365.20	6.60	72.00	92.70	2.60
R AITKEN	361.40	4.40	98.70	84.20	34.20
Al BROWN	353.40	17.50	53.40	90.60	5.40
Ang BROWN	341.80	39.10	128.30	76.50	8.10
Ed BURGASS	106.40	100.30	354.90	23.30	1.70
Y CAMERON	338.00	15.60	131.50	78.80	6.00
K McKENZIE	434.60	1.00	52.80	95.30	12.29
P CADDICK	368.30	11.30	154.80	94.00	3.90
R DONAGHUE	386.70	8.30	121.20	91.60	8.30
H ENGLEMAN	390.10	17.90	134.40	93.30	6.77
K STEDUL	358.50	23.40	84.30	83.80	1.68
C LEITH	391.20	9.70	120.60	93.10	2.76
MD COOPER	328.90	48.30	113.90	74.90	4.38
G CLABBIE	313.50	10.20	78.10	73.80	64.11
M BRICKELL	315.80	6.80	258.70	74.00	2.30
G BOYD	423.20	8.60	96.60	96.00	4.82
I LAURIE	395.10	13.00	80.80	92.30	7.14
D SKUDLAERK	378.70	30.90	68.60	86.30	1.58
A BOWMAN	350.50	48.50	117.90	81.50	4.79
C HOY	399.50	23.40	173.80	89.00	5.55
J DEAS	93.70	15.20	192.20	22.50	14.70
J BURNS	318.10	22.50	66.50	71.80	14.30
K BOYD	399.70	25.10	183.60	80.30	0.10
W BEIRNE	186.40	18.60	85.40	44.60	5.78
L CHEYNE	279.10	26.00	297.50	62.70	1.07
Y BOWMAN	355.10	11.70	63.60	94.20	1.01
S CONNOLLY	250.00	80.40	101.00	59.50	14.16
J DALEY	103.20	5.30	76.00	46.40	3.30
HM ARNOT	391.60	13.40	76.80	91.70	4.00
K CLYNE	385.20	16.50	121.50	90.40	9.35
R DEWES	408.90	4.10	111.30	93.60	1.17
G CHRISTIE	400.40	15.60	72.40	94.20	3.60
S BERNARD	392.90	8.40	137.20	93.10	0.50
D ARMET	406.40	10.30	98.60	92.60	5.40
M CONNOLLY	308.00	30.60	96.70	83.10	7.40
G ASPINALL	310.70	25.00	120.20	85.30	5.80
A BERRY	363.70	28.90	110.00	83.00	4.90

Table 15: Arousal scorings in controls

CONTROL	3SECA	CHESHIRE AR	ASDA AR	REV1.5AR
E BRYSON	29.46	10.20	31.93	30.37
C COLEY	21.73	11.35	21.03	30.50
A DARBYSHIRE	26.20	23.80	25.42	36.81
C HARKESS	24.09	9.30	23.35	31.38
G BAIRD	14.17	6.90	13.60	24.81
SA BAIRD	14.64	6.90	12.34	15.70
D BARRIE	22.67	15.90	21.57	22.87
C BARLEE	16.25	10.10	20.35	16.74
S ARTHUR	14.97	14.60	14.06	15.28
J ARKLEY	15.41	7.60	12.17	15.61
Y AITKEN	14.91	6.90	11.47	25.39
G BEAN	21.32	22.90	24.18	25.63
S HOOI	13.01	11.20	10.08	14.99
R BURGASS	14.66	9.80	10.45	27.26
M BROWN	25.74	21.90	28.92	27.74
R BROWN	23.08	21.50	30.41	24.12
N CLARK	12.69	7.07	12.14	25.41
J ABERDOUR	29.92	29.70	43.87	42.14
R AITKEN	32.87	23.91	36.86	35.53
Al BROWN	17.49	8.20	12.22	19.34
Ang BROWN	18.26	8.80	19.31	21.04
Ed BURGASS	48.63	38.30	47.47	55.81
Y CAMERON	15.44	10.80	14.85	17.55
K McKENZIE	21.12	19.47	19.33	22.56
P CADDICK	15.67	8.80	15.07	27.57
R DONAGHUE	17.38	10.20	11.95	18.64
H ENGLEMAN	17.69	6.61	13.23	19.32
K STEDUL	23.09	18.41	20.92	23.85
C LEITH	13.50	5.37	13.50	13.84
MD COOPER	26.63	9.49	25.72	28.19
M BRICKELL	15.58	14.60	16.15	16.11
G BOYD	13.39	9.36	12.62	25.32
I LAURIE	15.34	7.59	13.06	16.58
D SKUDLAERK	14.13	7.61	12.20	26.15
A BOWMAN	2.91	2.23	6.16	3.41
C HOY	12.16	10.21	16.67	13.40
J BURNS	22.11	13.20	21.40	33.40
K BOYD	13.29	8.10	12.73	25.68
L CHEYNE	24.29	5.16	23.86	27.20
Y BOWMAN	14.19	7.26	16.22	15.54
S CONNOLLY	23.76	12.24	18.72	27.21
HM ARNOT	16.83	12.20	16.21	29.26
K CLYNE	10.44	8.25	7.17	11.86
R DEWES	13.21	10.56	14.82	14.71
G CHRISTIE	5.84	5.40	8.09	6.47
S BERNARD	9.93	5.00	9.77	10.78
D ARMET	22.10	13.40	21.39	19.62
A BELL	24.39	8.80	23.65	31.48
J DALEY	36.49	20.00	38.37	41.90
W BEIRNE	30.58	17.36	23.18	32.90
G CLABBIE	63.13	66.60	61.73	74.96
J DEAS	47.03	33.30	45.90	54.25
M CONNOLLY	29.70	24.60	28.87	31.33
G ASPINALL	41.50	31.80	40.46	43.63
A BERRY	15.00	7.40	14.42	16.83

Table 16: Desaturation data in controls

CONTROLS	Deset2%/hr	Desat3%/hr	Desat4%/hr
A.BELL	2.40	1.00	0.60
C COLEY	1.20	0.70	0.30
A DARBYSHIRE	2.00	1.10	0.70
J DALEY	2.70	2.10	1.60
C.HARKESS	1.40	0.60	0.50
G.BAIRD	1.70	0.50	0.50
SA.BAIRD	0.30	0.00	0.00
D BARRIE	0.00	0.00	0.00
C BARLEE	0.40	0.10	0.00
HM ARNOT	1.10	0.70	0.40
S ARTHUR	2.00	0.80	0.30
J ARKLEY	2.60	1.30	0.80
Y AITKEN			
G BEAN			
S HOOI	12.00	7.10	6.00
Y BOWMAN	0.90	0.20	0.00
R BURGASS	1.30	0.80	0.30
A BOWMAN	0.00	0.00	0.00
M CONNOLLY			
S BERNARD	1.00	0.70	0.40
M BROWN	2.30	0.50	0.40
J ABERDOUR	3.60	0.40	0.30
J.DEAS	0.30	0.10	0.00
Ang Brown	1.80	0.20	0.10
Ed BURGASS	8.90	6.40	4.60
Y CAMERON	1.50	0.70	0.40
G ASPINALL			
R BROWN	7.50	3.80	1.60
P CADDICK	1.80	0.60	0.00
R DONAGHUE	6.00	3.80	2.10
E BRYSON	2.60	0.90	0.50
M BRICKELL	3.00	1.50	0.50
D ARMET			
K BOYD	1.20	0.30	0.20
C HOY	1.80	0.40	0.10
J BURNS			
Al BROWN	4.90	4.00	1.00
DAVID SEKUD	2.30	1.40	0.80
G CLABBIE	37.00	34.20	20.40
W BEIRNE	2.10	0.60	0.30
G BOYD	5.70	3.00	1.40
I LAURIE	4.00	1.50	1.00
R AITKEN	8.30	3.90	2.10
C LEITH	0.40	0.00	0.00
Dr MD COOPER	0.90	0.10	0.10
K MEKENZIE	0.70	0.00	0.00
K STEDUL	5.50	5.40	2.70
N CLARK	1.10	0.30	0.00
R DEWES	1.50	0.30	0.00
H ENGLEMAN	3.90	2.10	1.70
S CONNOLLY	5.40	2.10	0.60
A BERRY			
G CHRISTIE	3.10	2.00	0.70
K CLYNE	3.20	2.30	0.40
L CHEYNE	0.70	0.00	0.00

Table 17: BMI and age of matched pairs-case control study

RELATIVES	RAGE	RBMI	CTRLS	CAGE	CBMI
B.COLLINS	58.00	24.97	A.BELL	64.00	25.04
J.SCHOFIELD	27.00	22.59	E BRYSON	32.00	21.22
A.IRONS	21.00	23.93	C COLEY	23.00	22.10
S.FAIRWEATHER	28.00	23.42	A DARBYSHIRE	30.00	20.53
D.SIMPSON	45.00	21.33	C.HARKESS	23.00	31.60
A.AITKEN	21.00	22.16	G.BAIRD	22.00	20.45
S.WILLIAMS	24.00	19.44	SA.BAIRD	25.00	18.52
D.SILLET	41.00	26.73	D BARRIE	37.00	25.43
J SPOWART	30.00	25.14	C BARLEE	28.00	23.53
Rob SELF	20.00	21.86	S ARTHUR	30.00	23.30
S.AITKEN	18.00	22.14	J ARKLEY	20.00	21.91
K.LAFFERTY	20.00	27.81	Y AITKEN	26.00	26.67
G.AITKEN	21.00	25.05	G BEAN	23.00	22.16
GH.KERR	24.00	25.92	S HOOI	25.00	24.30
B ORROCK	28.00	26.23	R BURGASS	32.00	22.22
D.TAYLOR	50.00	29.24	M BROWN	57.00	20.07
I.TAYLOR	52.00	21.51	R BROWN	58.00	29.75
Col.IRELAND	36.00	31.79	N CLARK	31.00	32.70
I.DEMPSTER	46.00	26.79	J ABERDOUR	34.00	23.12
G.WILLIAMS	65.00	28.40	R AITKEN	58.00	25.50
E.IMRAY	22.00	23.95	Al BROWN	29.00	27.90
S PAXTON	28.00	25.84	Ang BROWN	28.00	22.16
S WILSON	31.00	23.87	Ed BURGASS	34.00	21.48
A WOOD	45.00	32.31	Y CAMERON	23.00	28.34
C KERR	54.00	28.28	K McKENZIE	51.00	28.48
R HAY	31.00	22.62	P CADDICK	29.00	21.33
D McCONACHIE	43.00	29.40	R DONAGHUE	52.00	29.09
C McMICHAEL	32.00	22.10	H ENGLEMAN	30.00	21.83
K MUIR	33.00	19.95	K STEDUL	26.00	22.80
K MOUNTAIN	43.00	24.39	C LEITH	23.00	23.51
S WALKER	28.00	21.22	MD COOPER	29.00	20.57
J HAWKINS	73.00	27.80	G CLABBIE	70.00	27.94
D MILROY	29.00	27.61	M BRICKELL	30.00	22.72
M MCCAULEY	33.00	22.32	G BOYD	26.00	21.34
P TINDALL	44.00	23.42	I LAURIE	42.00	23.92
J DOCHERTY	40.00	21.23	D SKUDLAERK	30.00	23.15
D WARD	41.00	24.98	A BOWMAN	34.00	22.40
JE MUNCIE	16.00	20.09	C HOY	17.00	21.56
J BOGIE	46.00	25.66	J.DEAS	63.00	27.43
S PIGGOT	30.00	23.42	J BURNS	23.00	24.98
M McCONACHIE	44.00	22.16	K BOYD	29.00	23.10
T PETTIGREW	65.00	23.81	W BEIRNE	71.00	22.10
S CRAWFORD	39.00	21.71	L CHEYNE	33.00	21.45
M TAIT	59.00	38.46	Y BOWMAN	34.00	30.09
J STARK	17.00	18.29	S CONNOLLY	35.00	22.66
A PETTIGREW	62.00	19.57	J DALEY	64.00	24.59
N STARK	20.00	22.28	HM ARNOT	30.00	24.07
Mag BROWN	49.00	25.91	K CLYNE	44.00	22.50
J HEWITT	30.00	27.80	R DEWES	24.00	25.14
H ARMOUR	18.00	20.66	G CHRISTIE	24.00	23.08
S ARMOUR	22.00	20.75	S BERNARD	27.00	27.78

Table 18: Selected questionnaire data-case control study

SUBJECT	GROUP	SMOKE	ALCOHL	CHOKE	BEDPART	APNEAS	SNORING	EDS
B COLLINS	REL	N	2	N	N	NR	N	N
J SCHOFIELD	REL	N	8	N	Y	N	N	N
A IRONS	REL	N	1	N	Y	N	N	Y
S FAIRWEATHER	REL	EX	7	N	N	N	N	Y
D SIMPSON	REL	C	13	Y	N	Y	Y	Y
A AITKEN	REL	N	20	N	Y	N	N	Y
S WILLIAMS	REL	N	1	N	N	NR	Y	N
D SILLET	REL	N	17	N	Y	N	Y	Y
J SPOWART	REL	N	1	N	Y	N	N	N
K LAFFERTY	REL	N	0	N	N	NR	N	Y
G AITKEN	REL	N	20	N	N	NR	N	Y
D TAYLOR	REL	C	13	N	Y	N	N	N
I TAYLOR	REL	N	20	N	Y	N	N	N
Col IRELAND	REL	EX	5	Y	Y	N	N	Y
S WILSON	REL	N	3	N	Y	N	N	Y
B ORROCK	REL	C	8	N	Y	N	N	Y
GW IRELAND	REL	EX	22.5	N	Y	N	N	Y
GH KERR	REL	N	3	Y	Y	N	N	Y
E IMRAY	REL	N	14	N	N	NR	N	Y
A WOOD	REL	C	7	N	Y	NR	Y	Y
JE MUNCIE	REL	N	0	N	N	NR	Y	N
M McCONACHIE	REL	C	28	Y	N	NR	Y	N
S AITKEN	REL	N	0	N	N	NR	N	N
JA BOGIE	REL	C	0	N	Y	N	Y	N
D MILROY	REL	N	12	Y	Y	Y	Y	Y
C McMICHAEL	REL	EX	0	Y	Y	N	N	N
D McCONACHIE	REL	N	24	N	N	NR	Y	N
K MOUNTAIN	REL	N		N	Y	N	Y	Y
R HAY	REL	C	27	Y	Y	N	Y	Y
K MUIR	REL	N	1	N	Y	N	Y	N
S WALKER	REL	N	4	N	Y	N	N	Y
S PAXTON	REL	EX	4	N	Y	N	Y	Y
M McCAULEY	REL	N	8	N	Y	N	N	N
S PIGGOT	REL	C	2	N	Y	N	Y	Y
D WARD	REL	C		N	Y	N	Y	Y
J HAWKINS	REL	EX	0	N	NR	NR	Y	Y
P TINDALL	REL	N	2	N	Y	N	Y	N
J DOCHERTY	REL	C	12	N	Y	N	N	Y
C KERR	REL	N	15	Y	Y	Y	Y	Y
Rob SELF	REL	N	0	N	N	NR	Y	Y
M TAIT	REL	N	4	N	Y	N	N	Y
J HEWITT	REL	N	14	N	Y	N	Y	Y
A PETTIGREW	REL	C	1	N	Y	N	Y	N
T PETTIGREW	REL	C	12	N	Y	Y	Y	N
N STARK	REL	C	0	N	Y	N	Y	N
Mag BROWN	REL	EX	11	N	Y	N	N	N
H ARMOUR	REL	N	3	N	N	N	N	N
S ARMOUR	REL	N	0	N	N	NR	N	N
J STARK	REL	C	9	N	N	NR	Y	Y
S CRAWFORD	REL	N	6	N	Y	N	N	N
A BELL	CTRL	N	9	N	N	NR	N	N
E BRYSON	CTRL	N	15	N	Y	N	N	N
C COLEY	CTRL	N	8	N	N	N	N	Y
A DARBYSHIRE	CTRL	N	1	N	Y	N	N	N

Table 18: continued...

J DEAS	CTRL	EX	19	N	N	NR	NR	N
J DALEY	CTRL	EX	23	N	N	NR	N	N
C HARKESS	CTRL	N	0	N	N	NR	N	N
G BAIRD	CTRL	N	8	N	Y	N	N	Y
SA BAIRD	CTRL	N	4	N	Y	N	N	N
D BARRIE	CTRL	EX	14	N	Y	N	N	N
C BARLEE	CTRL	N	1	N	Y	N	N	N
HM ARNOT	CTRL	C	30	N	Y	N	N	Y
S ARTHUR	CTRL	C	0	N	Y	N	N	N
J ABERDOUR	CTRL	N	12	N	Y	N	Y	N
C HOY	CTRL	N	0	N	N	NR	N	N
S BERNARD	CTRL	N	6	N	Y	N	N	Y
J ARKLEY	CTRL	C	6	N	Y	N	N	N
Ang BROWN	CTRL	EX	8	N	Y	N	Y	N
Alice BROWN	CTRL	N	10	N	Y	N	Y	Y
P CADDICK	CTRL	N	0	N	Y	N	N	Y
Edith BURGASS	CTRL	N	2	N	Y	N	N	N
M BROWN	CTRL	N	0	N	Y	N	N	N
G BEAN	CTRL	N	26	N	Y	N	Y	Y
Y AITKEN	CTRL	C		N	N	NR	NR	N
R BROWN	CTRL	EX	17	N	Y	Y	Y	N
S HOOI	CTRL	N	0	N	N	N	NR	N
Y BOWMAN	CTRL	N	2	N	Y	N	N	Y
R BURGASS	CTRL	N	8	N	Y	N	N	N
M BRICKELL	CTRL	N	12	N	Y	N	N	N
A BOWMAN	CTRL	N	4	N	Y	N	N	N
R DONAGHUE	CTRL	N	16	N	Y	Y	Y	N
J BURNS	CTRL	N	0	Y	N	NR	N	Y
Y CAMERON	CTRL	N	3	N	Y	N	N	N
G CLABBIE	CTRL	C	22	N	Y	N	N	N
K BOYD	CTRL	N	12	N	Y	N	N	Y
W BEIRNE	CTRL	EX	0	N	N	NR	N	N
R AITKEN	CTRL	N	1	N	Y	N	N	Y
G BOYD	CTRL	N	3	N	Y	N	N	N
D SZKUDLAREK	CTRL	EX	0	N	N	NR	N	N
I LAURIE	CTRL	EX	2.5	N	Y	N	Y	N
K STEDUL	CTRL	N	7	N	N	NR	N	Y
H ENGLEMAN	CTRL	C	5	N	Y	N	N	N
R DEWES	CTRL	N	26	N	Y	N	N	Y
N CLARK	CTRL	N	4.5	N	Y	N	N	N
C LEITH	CTRL	C	19	N	Y	N	N	N
K McKENZIE	CTRL	EX	6	N	Y	N	N	Y
Dr MD COOPER	CTRL	N	3	N	N	NR	N	N
S CONNOLLY	CTRL	C	2	N	Y	N	N	N
K CLYNE	CTRL	N	0	N	Y	N	N	Y
L CHEYNE	CTRL	N	6	N	Y	N	N	Y
G CHRISTIE	CTRL	EX	10	N	Y	N	N	N

Table 19: Selected polygraphic data in matched relatives

RELATIVE	TST	SOL	REMLat	SE%	AHI
B COLLINS	250.50	15.90	154.90	56.80	14.90
J SCHOFIELD	346.70	13.60	126.00	79.00	6.60
A IRONS	386.00	22.70	84.10	84.80	16.17
S FAIRWEATHER	442.00	12.10	115.90	95.90	11.80
D SIMPSON	198.30	44.40	239.90	44.50	25.70
A AITKEN	334.20	30.60	186.80	80.90	3.10
S WILLIAMS	392.10	23.10	94.10	91.00	11.80
D SILLET	326.00	6.00	181.10	85.10	14.40
J SPOWART	364.60	6.00	179.60	84.40	7.70
Rob SELF	415.90	4.10	160.70	91.80	11.25
S AITKEN	321.40	43.90	48.50	86.20	2.80
K LAFFERTY	235.80	27.80	188.30	58.70	20.40
G AITKEN	294.60	10.30	197.10	81.10	2.40
GH KERR	421.50	3.20	137.70	94.70	9.40
B ORROCK	399.00	37.80	56.70	89.90	11.40
D TAYLOR	386.10	14.80	123.90	82.50	11.50
I TAYLOR	322.00	25.30	166.40	75.90	25.30
Col IRELAND	347.70	8.30	120.60	82.00	24.16
I DEMPSTER	362.20	12.30	195.10	82.10	26.70
G WILLIAMS	126.30	28.20	311.90	33.10	67.46
E IMRAY	304.60	46.90	58.40	72.50	16.40
S PAXTON	419.10	8.90	284.10	92.90	8.30
S WILSON	358.20	13.40	154.40	83.70	10.40
A WOOD	343.80	21.50	80.10	81.50	18.00
C KERR	409.50	0.70	154.60	94.30	27.99
R HAY	330.10	38.50	171.60	75.50	15.50
D McCONACHIE	336.30	45.30	184.80	75.70	58.30
C McMICHAEL	389.30	33.50	97.00	90.10	9.40
K MUIR	395.80	21.30	63.10	89.60	12.73
K MOUNTAIN	392.40	6.00	111.00	91.20	19.42
S WALKER	397.60	11.50	77.00	91.00	9.36
J HAWKINS	205.20	29.00	242.70	48.90	21.05
D MILROY	353.60	28.00	104.50	83.20	4.20
M McCAULEY	370.80	11.40	92.90	88.70	6.47
P TINDALL	351.70	8.90	149.80	84.10	16.21
J DOCHERTY	428.40	15.30	68.60	95.40	4.48
D WARD	392.40	11.70	74.90	88.20	8.87
JE MUNCIE	414.10	5.80	255.40	87.90	6.09
J BOGIE	384.60	13.70	78.40	88.20	15.60
S PIGGOT	414.50	5.80	201.10	90.30	7.40
M McCONACHIE	271.60	48.10	62.00	75.90	24.50
T PETTIGREW	310.60	31.70	41.60	74.70	16.04
S CRAWFORD	371.20	14.20	120.20	88.00	7.44
M TAIT	355.60	7.20	277.70	84.90	88.25
J STARK	361.30	45.00	47.20	86.00	5.65
A PETTIGREW	318.70	18.10	63.50	76.60	23.70
N STARK	366.50	14.10	60.00	92.30	11.30
Mag BROWN	346.30	8.20	143.80	77.50	36.04
J HEWITT	358.10	5.20	83.00	85.30	16.08
H ARMOUR	346.80	34.10	105.80	82.20	9.17
S ARMOUR	334.50	17.10	138.40	79.60	14.71

Table 20: Selected polygraphic data in matched controls

CONTROL	TST	SOL	REMLat	SE%	AHI
A BELL	190.90	69.20	123.00	46.00	2.20
E BRYSON	340.10	26.00	130.20	86.50	0.90
C COLEY	274.70	22.30	121.90	61.90	0.00
A DARBYSHIRE	357.40	16.70	99.00	85.70	1.50
C HARKESS	201.80	27.20	310.20	51.70	1.20
G BAIRD	366.80	15.20	80.70	84.90	0.70
SA BAIRD	286.90	6.80	285.00	74.00	7.70
D BARRIE	325.50	35.60	96.00	78.80	2.40
C BARLEE	321.30	22.70	38.60	74.40	2.80
S ARTHUR	328.60	11.10	120.30	75.70	2.90
J ARKLEY	369.90	47.50	81.10	85.80	5.20
Y AITKEN	355.80	22.70	131.40	92.20	2.90
G BEAN	377.10	27.10	69.70	83.20	14.20
S HOOI	327.40	19.10	91.30	76.30	11.00
R BURGASS	402.10	19.20	68.00	91.60	3.90
M BROWN	358.90	30.80	178.50	81.70	7.20
R BROWN	335.40	14.70	139.80	76.40	13.20
N CLARK	407.90	3.90	81.50	93.80	5.88
J ABERDOUR	365.20	6.60	72.00	92.70	2.60
R AITKEN	361.40	4.40	98.70	84.20	34.20
Al BROWN	353.40	17.50	53.40	90.60	5.40
Ang BROWN	341.80	39.10	128.30	76.50	8.10
Ed BURGASS	106.40	100.30	354.90	23.30	1.70
Y CAMERON	338.00	15.60	131.50	78.80	6.00
K McKENZIE	434.60	1.00	52.80	95.30	12.29
P CADDICK	368.30	11.30	154.80	94.00	3.90
R DONAGHUE	386.70	8.30	121.20	91.60	8.30
H ENGLEMAN	390.10	17.90	134.40	93.30	6.77
K STEDUL	358.50	23.40	84.30	83.80	1.68
C LEITH	391.20	9.70	120.60	93.10	2.76
MD COOPER	328.90	48.30	113.90	74.90	4.38
G CLABBIE	313.50	10.20	78.10	73.80	64.11
M BRICKELL	315.80	6.80	258.70	74.00	2.30
G BOYD	423.20	8.60	96.60	96.00	4.82
I LAURIE	395.10	13.00	80.80	92.30	7.14
D SKUDLAERK	378.70	30.90	68.60	86.30	1.58
A BOWMAN	350.50	48.50	117.90	81.50	4.79
C HOY	399.50	23.40	173.80	89.00	5.55
J DEAS	93.70	15.20	192.20	22.50	14.70
J BURNS	318.10	22.50	66.50	71.80	14.30
K BOYD	399.70	25.10	183.60	80.30	0.10
W BEIRNE	186.40	18.60	85.40	44.60	5.78
L CHEYNE	279.10	26.00	297.50	62.70	1.07
Y BOWMAN	355.10	11.70	63.60	94.20	1.01
S CONNOLLY	250.00	80.40	101.00	59.50	14.16
J DALEY	103.20	5.30	76.00	46.40	3.30
HM ARNOT	391.60	13.40	76.80	91.70	4.00
K CLYNE	385.20	16.50	121.50	90.40	9.35
R DEWES	408.90	4.10	111.30	93.60	1.17
G CHRISTIE	400.40	15.60	72.40	94.20	3.60
S BERNARD	392.90	8.40	137.20	93.10	0.50

Table 21: Desaturation data in matched pairs

RELATIVES	R2%	R3%	R4%	CTRLS	C2%	C3%	C4%
B.COLLINS	3.40	1.90	1.40	A.BELL	2.40	1.00	0.60
J.SCHOFIELD	1.80	0.80	0.30	E BRYSON	2.60	0.90	0.50
A.IRONS	3.10	1.90	1.20	C COLEY	1.20	0.70	0.30
S.FAIRWEATHER	1.40	0.90	0.10	A DARBYSHIRE	2.00	1.10	0.70
D.SIMPSON	7.10	3.90	1.00	C.HARKESS	1.40	0.60	0.50
A.AITKEN	2.50	1.70	1.00	G.BAIRD	1.70	0.50	0.50
S.WILLIAMS	0.00	0.00	0.00	SA.BAIRD	0.30	0.00	0.00
D.SILLET	1.40	0.90	0.60	D BARRIE	0.00	0.00	0.00
J SPOWART	3.10	1.10	0.70	C BARLEE	0.40	0.10	0.00
Rob SELF	5.60	1.30	0.50	S ARTHUR	2.00	0.80	0.30
S.AITKEN	1.90	1.00	0.20	J ARKLEY	2.60	1.30	0.80
GH.KERR	0.80	0.70	0.50	S HOOI	12.00	6.10	5.00
B ORROCK	1.70	0.40	0.10	R BURGASS	1.30	0.80	0.30
D.TAYLOR	5.50	3.10	1.40	M BROWN	2.30	0.50	0.40
I.TAYLOR	6.70	2.70	1.10	R BROWN	7.50	2.80	1.60
Col.IRELAND	7.30	5.90	3.70	N CLARK	1.10	0.30	0.00
I.DEMPSTER	6.50	4.60	3.50	J ABERDOUR	3.60	0.40	0.30
G.WILLIAMS	11.70	8.10	4.60	R AITKEN	8.30	3.20	2.10
E.IMRAY	3.60	2.10	1.30	Al BROWN	4.90	2.00	1.00
S PAXTON	9.30	4.00	2.80	Ang Brown	1.80	0.20	0.10
S WILSON	2.10	0.70	0.60	Ed BURGASS	8.90	5.00	4.60
A WOOD	5.30	3.60	2.60	Y CAMERON	1.50	0.70	0.40
C KERR	19.70	15.00	7.70	K MEKENZIE	0.70	0.00	0.00
R HAY	4.80	1.50	0.80	P CADDICK	1.80	0.60	0.00
D McCONACHIE	43.20	38.80	27.80	R DONAGHUE	6.00	2.80	2.10
C McMICHAEL	8.80	7.10	2.70	H ENGLEMAN	3.90	2.10	1.70
S PIGGOT	5.30	3.40	1.90	K STEDUL	0.00	0.00	0.00
K MOUNTAIN	8.20	6.80	1.80	C LEITH	0.40	0.00	0.00
S WALKER	3.40	2.20	1.50	Dr MD COOPER	0.90	0.10	0.10
J HAWKINS	10.00	6.60	3.00	G CLABBIE	37.00	26.00	20.40
D MILROY	3.40	1.90	0.70	M BRICKELL	3.00	1.50	0.50
M MCCAULEY	2.90	2.00	1.70	G BOYD	5.70	3.00	1.40
M MCCONACHIE	7.30	2.70	1.00	K BOYD	1.20	0.30	0.20
P TINDALL	7.20	3.90	1.20	I LAURIE	4.00	1.50	1.00
J DOCHERTY	1.00	0.10	0.10	DAVID SEKUD	2.30	1.40	0.80
D WARD	0.80	0.10	0.00	A BOWMAN	0.00	0.00	0.00
JE MUNCIE	1.00	0.30	0.20	C HOY	1.80	0.40	0.10
J BOGIE	9.40	5.10	2.50	J.DEAS	0.30	0.10	0.00
J STARK	3.40	1.40	0.90	S CONNOLLY	5.40	1.10	0.60
M TAIT	32.90	26.20	16.30	Y BOWMAN	0.90	0.20	0.00
J HEWITT	3.00	1.00	0.70	R DEWES	1.50	0.30	0.00
A PETTIGREW	9.00	4.60	2.50	J DALEY	2.70	2.10	1.60
N STARK	2.50	0.80	0.50	HM ARNOT	1.10	0.70	0.40
Mag BROWN	3.20	1.60	0.90	K CLYNE	3.20	2.30	0.40
K.LAFFERTY	4.90	1.10	1.00	G CHRISTIE	3.10	2.00	0.70
S ARMOUR	1.00	0.20	0.00	S BERNARD	1.00	0.70	0.40
T PETTIGREW	1.90	0.60	0.30	W BEIRNE	2.10	0.60	0.30
S CRAWFORD	2.90	1.00	0.30	L CHEYNE	0.70	0.00	0.00

Table 22: Acoustic reflectance data in matched relatives

RELATIVES	ROPJ	RMPA	RGLO	RAPA	RPV
B COLLINS	1.90	3.20	1.60	2.40	22.90
J SCHOFIELD	1.10	2.50	1.70	1.80	15.90
A IRONS	1.70	3.20	2.00	2.40	14.20
S FAIRWEATHER	1.70	2.50	1.60	1.90	20.30
D SIMPSON	1.10	2.10	1.20	1.50	13.80
A AITKEN	1.80	4.10	2.10	2.80	31.00
S WILLIAMS	1.30	2.10	1.40	1.80	18.10
D SILLET	1.30	2.30	1.60	2.00	14.70
J SPOWART	1.70	3.30	2.70	2.70	22.00
Rob SELF	2.40	2.70	1.60	2.30	19.30
S AITKEN	1.30	2.50	1.60	1.90	17.10
K LAFFERTY	1.60	2.50	1.30	2.10	13.80
G AITKEN	2.10	2.50	1.50	2.10	20.40
GH KERR	1.40	2.00	1.70	1.70	20.50
D TAYLOR	2.00	2.20	1.30	1.80	11.00
I TAYLOR	2.10	3.20	2.30	2.80	23.50
Col IRELAND	1.70	2.80	1.50	2.20	17.40
I DEMPSTER	2.40	3.20	2.00	2.70	32.60
G WILLIAMS	2.10	3.10	1.30	2.30	28.60
E IMRAY	2.30	2.40	1.40	2.00	20.40
S PAXTON	1.60	2.70	2.50	2.40	15.30
A WOOD	1.90	2.00	1.50	1.90	13.10
C KERR	2.20	2.90	2.20	2.60	19.30
R HAY	2.20	2.90	2.10	2.50	20.20
D McCONACHIE	1.80	1.90	1.20	1.80	17.10
K MUIR	0.60	1.20	1.20	0.90	7.80
J HAWKINS	2.00	2.30	1.40	2.00	16.60
D MILROY	1.40	2.10	1.30	1.80	16.70
P TINDALL	1.30	2.70	2.00	2.10	15.70
J DOCHERTY	2.10	2.80	1.80	2.50	23.70
D WARD	2.20	2.90	1.50	2.20	27.40
J BOGIE	1.70	3.90	2.50	2.80	29.30
S PIGGOT	2.40	4.20	2.50	2.90	20.40
M McCONACHIE	1.50	2.10	1.30	1.70	20.40
T PETTIGREW	0.90	2.50	1.70	1.90	15.90
S CRAWFORD	1.90	2.40	1.60	2.20	18.40
M TAIT	1.40	1.90	1.30	1.50	11.80
J STARK	1.40	2.80	1.50	2.10	14.80
A PETTIGREW	1.40	4.10	2.50	2.90	30.30
N STARK	1.70	2.70	1.30	2.20	20.00
Mag BROWN	2.60	2.80	1.40	2.30	18.10
J HEWITT	1.60	3.80	2.70	2.90	23.20
H ARMOUR	2.00	2.70	1.70	2.40	20.40
S ARMOUR	1.90	2.30	1.80	2.10	13.80

Table 23: Acoustic reflectance data in matched controls

CONTROLS	COPJ	CMPA	CGLO	CAPA	CPV
A BELL	1.70	2.90	1.60	1.80	17.50
E BRYSON	1.30	2.50	1.50	1.90	17.00
C COLEY	1.90	3.30	1.70	2.40	18.00
C HARKESS	1.60	5.50	2.70	3.60	39.40
G BAIRD	1.10	1.40	1.00	1.20	13.00
SA BAIRD	1.30	2.40	2.10	2.10	19.70
D BARRIE	3.10	4.70	3.10	4.10	43.10
C BARLEE	1.20	3.30	2.50	2.30	14.90
S ARTHUR	1.90	2.60	1.60	2.10	19.10
J ARKLEY	1.60	3.80	2.00	2.60	21.00
Y AITKEN	2.30	3.00	1.50	2.40	20.50
G BEAN	1.60	2.40	2.30	1.80	17.90
S HOOI	2.10	3.50	2.70	2.70	30.20
R BURGASS	2.00	4.00	2.80	3.00	33.50
M BROWN	1.80	2.50	1.70	2.20	19.50
R BROWN	1.80	2.60	1.60	2.00	24.40
N CLARK	3.20	3.70	2.70	3.30	30.10
J ABERDOUR	2.00	3.10	2.20	2.60	23.70
R AITKEN	1.70	3.00	1.40	2.10	25.70
Al BROWN	1.60	2.10	1.80	2.00	24.50
Ang BROWN	1.60	3.00	2.20	2.30	25.70
Ed BURGASS	1.70	2.90	2.30	2.30	27.60
Y CAMERON	1.30	2.20	1.40	1.60	19.50
K McKENZIE	2.00	3.70	2.60	2.90	26.50
P CADDICK	1.80	2.20	1.40	1.80	21.70
R DONAGHUE	1.10	2.60	2.40	2.00	21.80
H ENGLEMAN	1.70	2.40	1.30	1.90	19.50
K STEDUL	1.60	3.10	2.50	2.50	24.10
C LEITH	2.10	2.80	1.40	2.30	25.20
MD COOPER	2.70	3.00	2.10	2.60	33.30
G CLABBIE	1.60	2.70	2.20	2.20	20.00
M BRICKELL	1.80	2.50	1.60	2.10	23.00
G BOYD	2.00	2.50	1.40	2.10	15.40
I LAURIE	1.60	2.40	1.80	1.80	19.30
D SKUDLAERK	0.90	2.50	2.40	2.00	21.80
A BOWMAN	1.60	3.50	2.20	2.60	31.00
J DEAS	1.60	1.70	1.20	1.50	12.30
K BOYD	2.30	2.90	1.40	2.30	27.70
W BEIRNE	2.30	2.80	1.50	2.30	20.40
L CHEYNE	1.80	2.70	2.10	2.30	22.80
S CONNOLLY	0.70	1.30	1.00	1.10	10.40
HM ARNOT	1.40	3.70	3.00	2.70	22.80
K CLYNE	2.60	3.60	2.70	2.90	38.10
R DEWES	1.90	2.80	1.70	2.30	25.20
G CHRISTIE	2.10	2.20	1.10	1.90	20.70
S BERNARD	1.60	2.20	1.40	1.80	20.80

Table 24: Selected cephalometrics in matched relatives

RELATIVES	GO-GN	UL	UW	PNS-PHW	SNA	SNB
B COLLINS	80.0	38.0	12.0	32.0	83.0	84.0
A IRONS	88.0	37.0	10.0	35.0	86.5	86.5
S FAIRWEATHER	85.5	43.5	11.0	32.0	86.0	88.0
D SIMPSON	89.5	52.0	15.0	30.0	81.5	77.5
A AITKEN	83.0	41.0	12.0	29.0	77.0	74.0
S WILLIAMS	88.0	43.5	8.0	31.5	82.5	79.5
D SILLET	80.5	50.0	13.0	36.0	81.0	81.0
J SPOWART	80.0	44.0	11.5	28.0	79.0	76.5
Rob SELF	89.0	39.0	11.5	29.0	77.0	74.5
S AITKEN	82.5	41.0	10.0	40.5	81.0	77.5
K LAFFERTY	82.5	50.0	13.0	30.0	84.0	84.0
G AITKEN	77.0	50.0	13.5	22.0	89.5	86.0
GH KERR	91.5	49.0	10.0	31.5	79.0	76.0
D TAYLOR	85.0	39.0	10.0	29.0	82.0	84.0
I TAYLOR	83.0	44.0	10.5	23.0	82.0	77.0
Col IRELAND	92.5	45.0	15.0	38.0	87.0	86.0
I DEMPSTER	85.0	45.0	15.0	34.0	86.0	81.0
G WILLIAMS	91.0	54.0	11.0	47.0	83.5	79.5
E IMRAY	90.0	41.0	10.0	27.0	81.0	83.0
S PAXTON	80.5	48.5	20.0	24.5	78.0	73.5
A WOOD	81.0	49.0	14.0	31.0	78.5	76.0
C KERR	90.0	41.0	14.0	30.0	85.5	83.0
R HAY	87.0	53.0	13.0	23.0	82.0	76.5
D McCONACHIE	77.0	43.0	13.5	25.0	80.0	78.0
K MUIR	75.0	49.0	10.0	27.0	80.0	73.5
K MOUNTAIN	78.5	43.0	11.0	21.0	84.0	82.0
J HAWKINS	85.0	44.0	11.0	29.0	73.5	69.5
D MILROY	86.5	40.0	13.0	25.0	79.0	82.0
P TINDALL	74.0	44.0	10.5	28.5	80.0	74.0
J DOCHERTY	84.0	42.0	13.0	30.5	74.0	71.0
D WARD	87.5	57.0	13.5	34.0	81.0	83.0
J BOGIE	83.0	50.0	12.5	27.5	84.0	81.0
S PIGGOT	80.0	44.0	12.5	30.0	80.0	73.0
M McCONACHIE	80.0	48.0	12.5	34.0	79.0	75.5
T PETTIGREW	100.5	40.0	13.0	23.0	84.0	83.0
S CRAWFORD	86.0	44.0	7.0	30.0	77.0	72.0
M TAIT	78.0	38.0	15.5	25.0	87.0	82.0
J STARK	75.5	39.0	13.0	20.0	83.5	76.5
A PETTIGREW	78.0	48.0	13.0	29.0	76.5	74.5
N STARK	85.0	48.0	11.0	30.0	85.0	81.5
Mag BROWN	80.5	40.0	8.0	30.0	76.0	73.0
J HEWITT	88.5	46.0	13.0	27.0	76.5	73.0

Table 25: Selected cephalometrics in matched controls

CONTROLS	GO-GN	UL	UW	PNS-PHW	SNA	SNB
A DARBYSHIR	84.0	38.0	7.0	30.0	86.0	81.5
C HARKESS	91.0	41.5	11.0	31.5	82.5	80.5
G BAIRD	78.5	40.0	7.0	30.0	79.5	76.5
SA BAIRD	82.0	33.5	11.0	32.5	91.0	87.5
D BARRIE	88.0	42.0	12.0	32.0	86.0	81.5
C BARLEE	86.0	51.0	9.0	40.5	79.0	77.5
S ARTHUR	90.0	44.0	12.0	30.0	90.5	87.5
J ARKLEY	89.0	44.0	8.0	30.0	84.0	81.0
G BEAN	82.0	43.0	13.0	30.0	83.0	79.0
S HOOI	89.0	42.0	12.0	32.0	87.0	84.0
R BURGASS	87.0	47.0	9.5	34.5	90.0	84.0
M BROWN	80.0	44.0	7.5	36.0	83.0	80.0
R BROWN	95.0	51.0	12.0	28.0	84.0	82.0
N CLARK	93.0	44.0	8.0	32.0	92.0	86.0
J ABERDOUR	91.5	39.0	12.0	30.0	78.0	78.0
R AITKEN	95.5	48.0	11.0	33.0	88.0	83.0
Ang BROWN	89.0	43.0	10.0	26.5	94.0	88.0
Y CAMERON	87.5	49.5	6.0	31.5	93.0	88.5
K McKENZIE	91.0	50.0	10.0	33.0	86.5	83.5
P CADDICK	88.0	41.0	10.5	31.0	94.0	89.0
R DONAGHUE	88.0	50.0	8.0	28.0	81.0	79.0
H ENGLEMAN	80.0	46.5	11.0	29.0	87.5	80.5
K STEDUL	88.0	38.0	10.5	32.5	88.0	83.0
C LEITH	95.0	41.0	12.0	35.0	89.0	83.0
MD COOPER	78.0	40.0	7.0	33.5	83.0	79.0
G CLABBIE	81.0	37.0	11.5	32.0	83.0	82.0
M BRICKELL	86.0	41.0	11.0	30.0	90.0	90.0
G BOYD	82.0	42.0	8.0	28.0	81.5	81.0
I LAURIE	80.5	42.0	9.5	35.5	80.0	75.0
D SKUDLAERK	98.0	49.0	10.0	32.5	86.0	83.0
A BOWMAN	83.0	48.0	12.0	31.0	91.0	83.0
J DEAS	89.0	39.0	11.0	49.0	86.0	83.5
K BOYD	91.5	44.0	12.0	33.5	86.0	82.0
W BEIRNE	87.5	40.0	10.5	31.5	86.5	85.5
L CHEYNE	77.0	38.5	7.5	32.0	91.5	85.0
Y BOWMAN	77.0	38.5	10.0	21.5	86.0	81.0
S CONNOLLY	88.5	33.5	12.5	31.5	85.0	82.5
HM ARNOT	87.5	51.0	10.5	36.0	80.0	82.5
K CLYNE	83.0	43.0	8.0	32.0	82.0	75.0
R DEWES	76.5	44.0	11.5	27.5	81.0	76.0
G CHRISTIE	85.0	42.0	6.0	32.0	82.0	83.5

Is the sleep apnoea/hypopnoea syndrome inherited?

Neil J Douglas, Marion Luke, Rajat Mathur

Abstract

***Background*—The aetiology of the sleep apnoea/hypopnoea syndrome (SAHS) is unclear in many patients. Snoring, a prerequisite for SAHS, runs in families. A study was carried out to determine whether there is an increased frequency of irregular breathing during sleep in relatives of patients with SAHS.**

***Methods*—A prospective study was performed of first degree relatives of 20 consecutive non-obese (BMI <30 kg/m²) patients with SAHS. Questionnaires on SAHS symptoms were sent to all first order relatives and those living within 150 miles of Edinburgh were invited for overnight monitoring of their breathing, sleep, and oxygenation patterns in the sleep laboratory.**

***Results*—Ten of the 40 relatives had more than 15 apnoeas + hypopnoeas/hour of sleep, and eight had more than five 4% desaturations/hour. These frequencies of irregular breathing and desaturation are significantly higher than in the British population. Cephalometric studies showed no skeletal abnormality but an increased uvular width was found in the affected relatives.**

***Conclusions*—There is an increased frequency of abnormal breathing during sleep in relatives of non-obese patients with SAHS.**

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The aetiology of the sleep apnoea/hypopnoea syndrome (SAHS)[1,2] in many patients is unclear. Snoring is a prerequisite for SAHS and is known to run in families. SAHS has been reported to run in two families[3,4] but this may have resulted from an association with obesity. We have therefore performed a pilot study to investigate the hypothesis that SAHS may be inherited. To avoid studying the inheritance of obesity we have used only index cases who were non-obese.

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Methods

Twenty consecutive new patients with SAHS (more than 15 apnoeas + hypopnoeas (A + H) per hour of sleep) with body mass index <30 kg/m² without evidence of gross retrognathia, hypothyroidism, or acromegaly took part in the study. These patients had a mean A + H frequency of 42/hour (range 17–76/hour), a mean body mass index of 27 kg/m² (range 24–29·5 kg/m²), and a collar size of 41·1 cm (range 39·4–44·4 cm). Each was asked to give details of all first degree relatives aged 18–75 years who were then sent a questionnaire relating to SAHS symptoms. All relatives who lived within 150 miles of Edinburgh were invited for a one night sleep study during which airflow at the mouth and nostrils was recorded by thermocouples, thoracoabdominal movement by induction stethogram, ear oxygen saturation by an Ohmeda Biox 3700 oximeter, and an electroencephalogram, electro-oculogram, and electromyogram were taken. Both sleep[5,6] and breathing pattern[6] were scored by standard criteria. All relatives attending for sleep studies had lateral cephalometry performed[7] from which standard bony and airway dimensions were measured.

Differences between groups were assessed by the unpaired Student's t test or χ^2 test as appropriate. Correlations were performed with SPSS-PC.

Results

Three of the 20 patients had no eligible first degree relatives. We thus tried to recruit all eligible relatives of 17 patients (15 men; mean (SD) BMI 27·4(1·6) kg/m²). They had 76 first degree relatives but 14 lived more than 150 miles from Edinburgh. Six of the eligible 62 relatives stated they were too ill to attend for sleep studies and 16 refused. Forty relatives (19 men) therefore had overnight sleep studies. Nine of the 22 relatives who were unable to participate came from one family.

Twenty one (12 men) of the 36 relatives who did not have sleep studies replied to the questionnaire. These had a significantly higher rate of loud snoring (15 of 21) than the attenders (13 of 40), but were no different in terms of witnessed apnoeas, daytime sleepiness, or other SAHS symptoms.

SLEEP STUDIES

Ten (nine men) of the 40 relatives had more than 15 A + H/hour of sleep (table). These "affected" relatives were older but were not more obese than the others. The affected

teristics of relatives with >15 A + H/hour of sleep or <15 A + H/hour of sleep

	>15 A + H/hour	<15 A + H/hour
	10	30
	9M, 1F	10M, 20F*
SD) age (y)	44 (4)	34 (2)†
SD) BMI (kg/m²)	27 (1)	25 (1)
ls hour	17 (11-23)	9 (7-11)*
. Sao_2(%)	81 (77-85)	87 (86-88)†
nin)	328 (303-353)	345 (327-363)
nin)	18 (10-26)	25 (16-34)
)	79 (72-86)	85 (80-90)

l—apnoeas + hypopnoeas; BMI—body mass index; lowest Sao_2—lowest oxygen ion overnight; TST—total sleep time; SOL—sleep onset latency; SEI—sleep ıcy index; *p < 0·01 v relatives with >15 A + H/hour. †p < 0·05 v relatives >15 A + H/hour. Values in parentheses are 95% confidence limits unless otherwise.

relatives had more frequent arousals from sleep and lower minimal oxygen saturations than the 30 unaffected relatives. Eight of the 40 relatives had more than five 4% desaturations/hour. Factors significantly correlated with abnormal breathing during sleep were sex, body mass index ($p < 0·001$), and age ($p < 0·05$), but not collar size.

QUESTIONNAIRES

Eight of the 10 affected relatives were described as loud snorers compared with five of the 30 unaffected ($p < 0·01$). Similarly, witnessed apnoeas were more common in affected relatives (5/8, 0/25, ($p < 0·01$)), but there was no increase in daytime sleepiness (2/10, 10/30).

CEPHALOMETRY

Cephalometric measurements were compared between the 10 affected relatives and 10 unaffected relatives matched by priority for sex, family (possible in three cases), and height. The only variables which were different in the affected relatives were the gonion-gnathion-hyoid angle (affected 30° (range 26–34°), unaffected 21° (range 19–23°); $p < 0·05$) and uvular width (12·7 mm (range 11·3–14·1 mm), 10·0 mm (range 9·2–10·8 mm); $p < 0·01$).

Discussion

This study shows that 10 of 40 first degree relatives of non-obese patients with SAHS had more than 15 A + H/hour of sleep. No control group was used in this pilot study because apnoeas, hypopnoeas, and desaturations are reproducibly scored by objective criteria,[4] and abnormal breathing during sleep is rare with a well described frequency in the British population.[9] The major control comparison for our study is a random sample of 893 middle aged British men[9] of whom 45 had more than five 4% desaturations/hour compared with eight of our 40 relatives ($p < 0·0001$, χ^2 test) or seven of our 19 male relatives ($p < 0·0001$). That study was performed with the same oximeter and a similar desaturation algorithm as was used in our study. The other comparison is with our previous report that none of 33 asymptomatic non-obese (BMI < 30 kg/m²) Edinburgh subjects had more than 15 A + H/hour of sleep[10] while eight of our 35 first order relatives who weighed <30 kg/m² had more than 15 A + H/hour of sleep, again indicating that our relatives had abnormal breathing during sleep ($p < 0·005$).

We do not think our finding of increased irregular breathing and desaturation during sleep in the relatives of non-obese patients with SAHS is affected by the recruitment of only 40 of 62 eligible relatives. In the nine families with 100% coverage, six of the 19 relatives (32%) had >15 A + H/hour of sleep. In addition, the increased rate of snoring among those relatives who did not attend for sleep studies suggests that they would have had an even higher frequency of irregular breathing than those relatives studied, and the fact that they were not studied biased against the positive findings of this study. Even if one assumed that all the 22 relatives who declined sleep studies had normal breathing during sleep, our relatives still had an increased frequency of desaturation ($p < 0·01$) and irregular breathing ($p < 0·05$).

Our conclusion is consistent with a simultaneous symptom questionnaire study reporting more daytime sleepiness and apnoeas in relatives of patients with SAHS.[11] Sleep studies were not performed, however, and families of patients with SAHS might be more aware of these features. Furthermore, the patients with SAHS were obese (mean (SD) BMI 37 (2) kg/m²), although the increased frequency of reported breathing pauses remained when adjustment was attempted for the body mass of the relatives.

Our cephalometric studies have not shown any primary skeletal abnormality in the affected relatives although, as there were only 10 affected relatives, confirmation of this finding is required in a larger number of subjects. The difference in uvular width may reflect either increased fat deposition[12] or mucosal or muscular changes[12] which, like the difference in gonion-gnathion-hyoid angle, may be secondary to abnormal breathing during sleep. The inherited abnormality may therefore be altered soft tissue or fat deposition in the neck or a defect of the control of upper airway calibre rather than an inherited skeletal defect.

This pilot study provides sufficient evidence of a familial predisposition to SAHS to warrant further more detailed studies.

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